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Guest Editorial by Dr Chris Fearne

Proportion of Surgical Patients Prescribed VTE Prophylaxis Upon Admission

Sacroiliac Joint Syndrome: A Multidisciplinary Perspective on Diagnosis and Management

Effects of Cardiozym™ Supplementation on Lipid Profile and Cardiovascular Risk in Patients at Risk for Cardiovascular Disease: A Retrospective Chart Review

Issue Guide

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The Editorial Board and the authors honour Prof. Felice's enduring legacy. In the great lineage of minds that shaped Maltese science, he stands as a giant, steady and inspiring.

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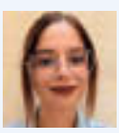

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Prof. Alex Felice MD PhD FMCPath(C Spec Genetika) KM was a pioneering Maltese geneticist who transformed haemoglobinopathy care, advanced molecular diagnostics, and mentored generations of scientists, leaving an enduring legacy in thalassaemia and rare disease research as well as national biomedical innovation.

GUEST EDITORIAL

DR CHRIS FEARNE

Antimicrobial Resistance

A Call to Action

One of the great medical successes of the last 100 years is the advent and widespread use of antimicrobials. Countless millions of lives have been saved, perilous surgical procedures have been made safe and, lifesaving, but immunocompromising, treatments have been made possible. However, the very ubiquitousness and, at times, inappropriate extensive use of these antimicrobials is threatening their effectiveness. With disastrous effects. The emergence of antimicrobial resistance (AMR) is a real global medical threat. Already today, within the European Union and OECD countries, it is estimated that 1 in 5 bacterial infections are resistant to antimicrobials.

Last year the Global Burden of Disease Study 2021 (GBD 2021) Antimicrobial Resistance Collaborators published their predictions in *The Lancet*.[1] Between 2025 and 2050 AMR will be directly responsible for 39 million global deaths. Meanwhile, the Organisation for Economic Co-operation and Development (OECD) are predicting that in 10 years' time a massive 90% of hospital-acquired bacterial infections will be resistant to antibiotics. Making hospitals and the way we deliver medical care today, obsolete. These are serious institutions pronouncing deadly serious statements.

Even worse, the problem extends beyond human health. Large-scale misuse of antibiotics as growth promoters in livestock has brought AMR into the animal sector. The World Organisation for Animal Health is warning that AMR will lead to animal production losses close to 1,000 billion euros over the next 20 years.[2] Leading in turn to issues of food security and increased hunger and poverty worldwide.

In the face of these existential threats, we need to act.

Malta has a National Action Plan for addressing Antimicrobial Resistance. And Malta has been actively campaigning for One Health action against AMR on a global level. (Last year, Malta was one of two co-facilitators bringing forward a United Nations General Assembly Declaration on AMR, which now forms the basis for global action).

But whilst AMR is a global problem, a large part of the solution is local.

Worryingly, the European Centre for Disease Control (ECDC) reports that Malta has very high usage of broad-spectrum antibiotics. The ratio of broad-spectrum to narrow-spectrum antibiotics is the second highest (after Hungary) in the EU/EEA region.[3] Indeed, third-generation cephalosporins, and macrolides are frequently prescribed in a primary care setting. Paradoxically, whilst close to 2/3 of streptococcal respiratory infections in Malta are resistant to macrolides, only 5% are resistant to amoxicillin.

It gets worse. The research and development pipeline for new antibiotics is almost empty. We are running out of effective antimicrobials much faster than we can produce new ones.

How can we do our part to mitigate against this impending "silent pandemic"?

1. Antibiotic stewardship. Mediterranean patients are known to feel unsatisfied unless they are prescribed a medicine for their illness (or their pet's). As professionals, we need to lead. Our patients' present and future safety depends on our professional guidance.

2. Veterinary services need support to ensure proper veterinary governance, including vaccination, of local livestock.
3. The National Action Plan (which incidentally also covers the agricultural sector) needs full funding. Good intentions on their own are not enough. On the other hand, the OECD estimate a 5-in-1 return on investment in productivity savings for every euro spent on combating AMR. In other words, prevention is not only better than cure, but also cheaper than cure.
4. Internationally, Malta needs to continue to lead in this sector. The setting up of an International Independent Scientific Panel on Evidence on AMR (much the same as with Climate Change) is a priority. Suffice it to say that according to the World Health Organisation (WHO) in 2022, 10% of the world's population regularly ate food irrigated with untreated wastewater.

We are the first generation to have lived our whole lives with the benefit of the universal use of antimicrobials. For the sake of our children and grandchildren, we have the scientific and moral duty to ensure we are not also the last.

1 www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)01867-1/fulltext
2 www.woah.org/app/uploads/2024/09/ecoamr-woah-animal-sector-web-reduced-23924.pdf
3 antibiotics.gov.mt/wp-content/uploads/2024/04/A4-booklet-2023.pdf

AUDIT

DR MARIAM ADEOLA OPADIYA, DR NASRI AHMED,
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Proportion of Surgical Patients Prescribed VTE Prophylaxis Upon Admission

INTRODUCTION

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), remains a significant cause of morbidity and mortality among hospitalized patients, particularly those undergoing surgery.[1] Postoperative patients are at an increased risk of developing VTE due to multiple factors, including immobility, endothelial damage, and changes in coagulation. Guidelines from international bodies such as the American College of Chest Physicians (ACCP) and the National Institute for Health and Care Excellence (NICE) recommend the use of pharmacological and mechanical prophylaxis for VTE in surgical patients, tailored to their risk profiles.[2]

Surgical patients, especially those undergoing major surgeries, are at heightened risk for thromboembolic events, leading to recommendations for risk assessment and timely prescription of thromboprophylaxis. Inadequate VTE prophylaxis in surgical settings can result in preventable complications. It has been shown that timely administration of prophylactic measures, including low molecular weight heparin (LMWH), unfractionated heparin (UFH), and mechanical methods such as graduated compression stockings, can significantly reduce the risk of VTE development.[3]

The ACCP guidelines suggest the use of pharmacological VTE prophylaxis in patients undergoing surgery who are at moderate to high risk for VTE, without contraindications such as active bleeding or history of recent cerebrovascular accidents (CVA). NICE guidelines recommend that all patients undergoing surgical procedures, particularly those who will have reduced mobility for a period postoperatively, should receive a risk assessment and appropriate VTE prophylaxis.[4] Studies have demonstrated that approximately 40-60% of hospital-acquired VTEs are preventable through appropriate prophylaxis, but there remains a considerable gap in practice, as evidenced by audits in various healthcare institutions.[3] Compliance with VTE prophylaxis guidelines often faces challenges related to preoperative planning, patient-specific contraindications, and breakdowns in communication between clinical teams.

BACKGROUND AND AIM

VTE is a significant medical concern, especially for patients undergoing surgical procedures. According to global health guidelines, patients admitted for surgery are at a higher risk for developing VTE due to factors such as reduced mobility, surgical trauma, and changes in blood clotting mechanisms. The audit's main aim is to evaluate the proportion of surgical patients at

Mater Dei Hospital prescribed VTE prophylaxis upon admission. The specific objectives of this audit are to assess compliance with established guidelines, specifically the NICE NG89,[4] identify barriers, enhance patient safety, develop recommendations and possibly monitor and review if these recommendations were adhered to in subsequent audits. By achieving these objectives, the audit aims to enhance the overall quality of care provided to surgical patients at Mater Dei Hospital and to align the hospital's practices with international standards for VTE prophylaxis.

METHODS

The audit employed a retrospective approach, examining data between June and August 2024, for patients older than 18 years. Information was collected from electronic records, specifically focusing on admission notes from the Emergency Department and subsequently, patient treatment charts. Each patient's record was meticulously reviewed to determine whether VTE prophylaxis was prescribed appropriately and in a timely manner. Although no formal proforma was used, data collection was guided by recommendations from the ACCP (9th edition) and NICE NG89 guidelines, which both advocate for VTE risk stratification upon admission using validated tools, followed by timely pharmacological and/or mechanical prophylaxis based on the individual's risk and contraindications.

RESULTS

A total of 23 patients were admitted for elective surgery, with 5 not receiving VTE prophylaxis. Additionally, 107 patients were admitted through the emergency department (ED), with a subset of patients not receiving VTE prophylaxis. The audit primarily focused on those patients who did not receive VTE prophylaxis, and these patients were grouped accordingly. The reasons for the omission of prophylaxis were then documented:

- **Total patient cohort:** 130 patients
- **Elective admissions:** 23 patients were direct admissions for elective surgery (DAF); only 5 of these did not receive VTE prophylaxis. The omission in these cases may be due to the type of surgery planned, and was deemed justified.
- **Emergency admissions:** 107 patients were admitted via the emergency department.
- **VTE prophylaxis given:** 76 patients (58%)
- **VTE prophylaxis not prescribed:** 54 patients (42%)

Breakdown of the 54 patients not prescribed VTE prophylaxis:

- **Emergency Surgery Cases (22 patients):** These patients underwent emergency surgical procedures, and the omission of VTE prophylaxis was justified based on the clinical context at the time of admission.
- **Contraindications (10 patients):** These included per rectal (PR) bleeding, hematuria, and intracranial haemorrhage or cerebrovascular accidents (CVA), where administering VTE prophylaxis could have worsened the condition. These were therefore considered justified omissions.
- **Elective Surgery Admissions (5 patients):** These direct elective admissions did not receive VTE prophylaxis initially; this was also justified in context.
- **No Reason Documented (17 patients):** 17 patients were not prescribed VTE prophylaxis despite no recorded contraindications or documented rationale. These patients did not undergo surgery, and some were later initiated on VTE prophylaxis 3 - 4 days after admission. The audit highlighted these cases as key areas for improvement, particularly in the documentation at the point of admission.

Prophylaxis Prescribed:

- A total of **76 patients (58%)** were prescribed VTE prophylaxis upon admission.
- Conversely, **54 patients (42%)** did not receive VTE prophylaxis at the time of admission.

DISCUSSION

These findings highlight a substantial proportion of surgical patients not receiving VTE prophylaxis upon admission, either due to valid clinical reasons or a lack of proper documentation and adherence to guidelines.

To address these findings, the following recommendations are proposed:

1. **Enhanced Education and Training:** Reinforce the importance of VTE prophylaxis among surgical teams, including education on identifying patients at risk and contraindications to VTE prophylaxis.
2. **Process Improvements:** Introduce systematic checks within the admission process to ensure VTE prophylaxis is considered and prescribed when appropriate.
3. **Regular Audits:** Implement regular follow-up audits to monitor adherence to guidelines and assess the impact of interventions on compliance rates.
4. **Interdepartmental Communication:** Strengthen communication channels between the emergency department, surgical teams, and pharmacy to ensure timely and accurate prescription of VTE prophylaxis.
5. **Documentation Improvements:** Improve documentation practices to ensure that all reasons for withholding VTE prophylaxis are clearly stated in patient records.
6. **Further Investigation into Contraindicated Prescriptions:** Although this audit focused on patients who did not receive VTE prophylaxis, we noted that a few patients were prescribed prophylaxis despite having documented contraindications. While this was outside the scope of our current analysis, it highlights a potential area of concern. Future audits should investigate such cases in greater detail to ensure that prophylaxis is not administered inappropriately, thereby enhancing patient safety and adherence to clinical guidelines.

By implementing these recommendations, Mater Dei Hospital can significantly enhance the quality of care for surgical patients and align its practices with international standards. Continuous monitoring and review will be crucial to ensuring sustained compliance and further improvements in patient safety.

CONCLUSION

The audit on the proportion of surgical patients prescribed VTE prophylaxis upon admission at Mater Dei Hospital reveals a need for significant improvement in adherence to established guidelines. Notably, 17 from 130 patients did not receive VTE prophylaxis without any documented justification. These findings may suggest inconsistencies in guideline implementation and documentation practices, warranting further evaluation and quality improvement measures.

Several barriers contributing to the under-prescription of VTE prophylaxis have been identified. These include incomplete documentation or omission of VTE risk assessments in the preoperative checklist, particularly for patients undergoing elective or emergency surgeries, where prophylaxis planning was either overlooked or delayed.

NICE GUIDELINE RESEARCH RECOMMENDATIONS

As highlighted in NICE guideline NG89, there are key areas where evidence is lacking and further research is essential to enhance patient safety and optimise prophylaxis strategies:

1. **Risk Assessment Tools:** The National VTE Risk Assessment Tool, although widely adopted across the NHS, has not been validated against other tools. Further studies are needed to assess its accuracy in identifying patients at risk of VTE or bleeding and compare it with alternative tools.
2. **LMWH Dosing in Obese Patients:** There is uncertainty about whether fixed-dose or weight-based dosing of LMWH is more effective in obese patients (BMI >35). Evidence based on clinical outcomes, not just biological markers, is needed to guide dosing and reduce unnecessary risks.
3. **Oral Anticoagulants for Lower Limb Immobilisation:** VTE is a known risk in patients with lower limb immobilisation. However, there is a lack of comparative evidence between oral anticoagulants and injectable options. Research into the safety and efficacy of oral anticoagulants in this group could improve outpatient care.
4. **Aspirin for Fragility Fractures:** Some studies suggest aspirin may be as effective as LMWH or fondaparinux for VTE prevention after fragility fractures, but evidence remains inconclusive. High-quality trials are needed to evaluate this low-cost alternative.
5. **Prophylaxis Duration Post-Hip Replacement:** Current recommendations for 28-day prophylaxis after hip replacement are based on limited evidence. Research should evaluate if shorter durations are equally effective, which may improve patient compliance and reduce healthcare costs.

Including these research priorities in future audits and clinical planning can support better VTE risk stratification, more effective prophylaxis, and enhanced patient outcomes.

REFERENCES

1. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng89 [Accessed April 1, 2025].
2. Abdalla YA, Kamil AM, Mohamed SAA, et al. Thromboprophylaxis in Patients Admitted to the Surgical Ward: Clinical Audit. Vasc Health Risk Manag 2023;19:651-656.
3. Ambra N, Mohammad OH, Naushad VA, et al. Venous Thromboembolism Among Hospitalized Patients: Incidence and Adequacy of Thromboprophylaxis - A Retrospective Study. Vasc Health Risk Manag 2022;18:575-587.
4. Lau BD, Haut ER. Practices to prevent venous thromboembolism: a brief review. BMJ Qual Saf 2014;23(3):187-95.

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SURVEAL PHARMA

DR PATRICK CHOUEIRY

Effects of Cardiozym™ Supplementation on Lipid Profile and Cardiovascular Risk in Patients at Risk for Cardiovascular Disease

A Retrospective Chart Review

ABSTRACT

INTRODUCTION

Numerous previous studies have examined the effects of dietary supplements on cardiovascular (CV) health, but there is limited research on the effects of combined nutraceuticals on lipid profile and CV risk.

OBJECTIVES

To investigate the effects of a novel nutraceutical product (Cardiozym™) containing red yeast rice (RYR, monacolin K), hydroxytyrosol (HT), and coenzyme Q10 (CoQ10) on lipid profile and CV risk.

METHODS

In this retrospective chart review, data were collected from the medical records of 38 patients at risk for cardiovascular disease (CVD) who were started on Cardiozym™. After 6 months of supplementation, the primary outcome was improvement in lipid profile and reduction in CVD risk as measured by the Framingham Risk Score (FRS). Health parameters and CV risk scores were compared between baseline and 6-month follow-up using a paired samples t-test. Linear mixed models adjusted for patient sex, age, weight, and use of antihypertensive medication were used to test the change in each parameter from baseline to follow-up.

RESULTS

Cardiozym™ had a significant beneficial effect on serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL) and non-high-density lipoprotein cholesterol. Improvements in blood pressure levels were also observed. Significant associations were found between alcohol consumption and changes in mean LDL and triglyceride levels. After adjustment for age, sex, weight, and use of antihypertensive medications, significant reductions in mean FRS and 10-year CV risk were observed.

CONCLUSIONS

A 6-month Cardiozym™ supplementation based on RYR, HT and CoQ10 not only improved lipid profile in subjects at risk of CVD but also mitigated CV risk, highlighting its effectiveness as an intervention to promote heart health.

KEYWORDS

CV Disease, Red Yeast Rice, Hydroxytyrosol, CoQ10, Framingham Risk Score, Lipid profile, Blood Pressure.

INTRODUCTION

Cardiovascular disease (CVD) in its various forms remains the leading cause of morbidity and death worldwide, particularly in developing countries, accounting for approximately 32% of all deaths in 2022.[1] Over the past 40 years, there has been a dramatic decline in CVD mortality, accompanied by major advances in the management and prevention of CVDs through pharmaceutical interventions, lifestyle modifications, and dietary supplements.[2]

Dietary supplements have received considerable attention as a potential adjunctive therapy in the management of various CVDs. Several research studies have examined the effects of dietary supplements on cardiovascular (CV) health, but the results have been inconsistent. For example, multivitamin supplementation has been shown to be ineffective in reducing the risk of CVD or mortality in the absence of a clear nutrient deficiency.[3,4] On the other hand, other compounds have shown promising effects in improving cardiac function and lowering blood pressure (BP) and lipids.

Among these compounds, Red Yeast Rice (RYR) produced by yeast fermentation of white rice, has been shown to possess cholesterol-lowering effects provided by its major bioactive compound, monacolin K. According to a recent review, significant reductions in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) levels were observed in patients with mild to moderate hypercholesterolemia following RYR supplementation, while effects on high-density lipoprotein cholesterol (HDL) and triglycerides (TG) were generally inconsistent.[5]

Coenzyme Q10 (CoQ10), a naturally occurring antioxidant, has been suggested to have cardioprotective effects due to its essential role in gene expression, energy metabolism and reduction of oxidative stress. Recent evidence has shown that CoQ10 supplementation prevents the oxidation of LDL and its accumulation in arteries, and reduces vascular stiffness and hypertension in patients with CVD.[6,7] More specifically, it significantly decreased TC and increased HDL levels without affecting TG and LDL levels.[8,9]

Current research has also highlighted the potential CV benefits of hydroxytyrosol (HT), a compound found in extra virgin olive oil with potent antioxidant and anti-inflammatory properties. According to a recent review, HT supplementation induced significant reductions in TC, LDL, and TG levels, while increasing HDL levels and preventing LDL particles stemming from oxidative damage.[10,11] Lower BP levels were also observed after HT supplementation.[10]

Combinations of these compounds are also available, but few studies have demonstrated their beneficial effects in combination therapy. D'Addato et al. reported that a combination of monacolin, CoQ10, HT and berberine improved the lipid pattern in hypercholesterolemic patients by reducing LDL and TG levels.[12] In hypertensive and hypercholesterolemic patients with metabolic syndrome, a formulation of RYR and CoQ10 reduced TC, TG, LDL, serum glucose, and BP, without affecting HDL levels.[13] In addition, a systematic review and meta-analysis of randomized controlled clinical trials of a nutraceutical combination including red yeast extract (monacolin K), CoQ10, in addition to folic acid, astaxanthin, policosanols, and berberine demonstrated improved serum levels of TC, TG, both HDL and LDL, and fasting blood glucose (FBG), without beneficial effects on BP.[14]

These studies highlight the beneficial effects of different combinations on lipid profile and BP levels in different patient populations. However, no previous studies have evaluated the effects of such combinations in terms of CV risk. Therefore, this study was designed to evaluate the effect of 6 months of Cardiozym™, a combined therapy of RYR, CoQ10 and HT, on patients' lipid profile, FBG, HbA1C and BP. In addition, the study aimed to evaluate the effect of Cardiozym™ on patients' CV risk using the Framingham Risk Score (FRS) and the 10-year risk of CVD, thereby adding valuable insights to the existing body of knowledge in the field of CV health.

METHODS

STUDY DESIGN AND SETTINGS

A retrospective chart review was performed in Malta between August 2020 and December 2022 and included patients initiated on Cardiozym™, a combination of RYR (200 mg, of which monacolin K 10 mg), CoQ10 (100 mg), and HT (5 mg), to evaluate the effects of Cardiozym™ administration. Data were extracted from patients' medical records at a baseline time point corresponding to the initial visit and at a follow-up time point 6 months after baseline.

STUDY PARTICIPANTS

Patients aged 20 years and older at risk for CVD and atherosclerosis or with a family history of CVD, atherosclerosis, and sudden death were enrolled. Patients with an indication for lipid-lowering therapy and those with borderline dyslipidemia were also included. Those with borderline dyslipidemia had an LDL between 130 mg/dl and 159 mg/dl. At-risk patients were those with an LDL > 160 mg/dl. Patients who had previously received statins and were intolerant of their treatment were also included in the study.

Exclusion criteria were patients under 20 years, familial hypercholesterolemia, allergy or contraindication to any of the components of Cardiozym™, pregnancy, active CVD, or a history of myocardial infarction (MI). Patients treated with statins or other lipid-lowering agents, such as fibrates or ezetimibe, and those taking lipid-lowering supplements were excluded from the study.

DATA COLLECTION AND OUTCOME MEASURES

Data from both the baseline and follow-up visits were extracted from patients' medical records using a case report form (CRF). At baseline, data collected included demographic information (age, sex, occupation), weight and height, and medical history (CVD, hypertension, diabetes, chronic kidney disease [CKD], cancer, and family history of CVD). In addition, the data collected included the lipid profile (TC, LDL, HDL, TG, non-HDL), FBG and HbA1C, BP measurements (systolic [SBP], and diastolic blood pressure [DBP]), lifestyle factors (smoking, alcohol consumption, menopause), and current medication use for antihypertensive drugs, corticosteroids, antiplatelet agents, and Framingham risk calculation. At the second visit, changes in any of the baseline characteristics were recorded.

The FRS was calculated for the total patient population based on the following coronary risk factors: age, sex, smoking, TC (mg/dl), HDL (mg/dl), SBP, and antihypertensive intake. The 10-year % risk of CVD in percentage was calculated using the Framingham score calculator and classified into three categories as low risk (< 10%), intermediate risk (10–20%), and high risk (> 20%) for developing CHD in the coming 10 years.

The study was an observational analysis of pre-existing medical records and did not involve direct contact with participants. However, each patient was assigned a unique identification number for this study to maintain the confidentiality and privacy of the data collected.

STATISTICAL METHODS

To summarize patient characteristics, means with standard deviations and frequencies with percentages were used to describe continuous variables and categorical variables, respectively. Two-tailed paired sample t-tests were used to compare changes from baseline for variables including lipid profile parameters and CV parameters. Separate multivariate linear regression models were used to evaluate the association between patient age, sex, weight, smoking and alcohol consumption and the change in LDL, TG, FBS, SBP, FRS, and the 10-year risk of CVD between baseline and follow-up. Baseline to follow-up changes in TC and LDL levels, SBP, FRS, and 10-year risk of CVD were evaluated using linear mixed models adjusting for age, sex, weight, and the use of antihypertensive medications.

A p-value <0.05 was considered statistically significant. All statistical analyses were performed using Stata v17.0 software.

RESULTS

PATIENT CHARACTERISTICS AT BASELINE AND FOLLOW-UP

Data from 38 patients were collected and analyzed. A summary of patient characteristics at baseline is shown in Table 1. The mean (standard deviation [SD]) age of the patients was 50.60 (11.38) years, and 63% were female. Common CVD risk factors included hypertension treated with antihypertensive drugs (21.1%), family history of CVD (50%), and sudden death (7.9%). At follow-up, patients' mean (SD) body weight decreased from 75.90 (12.13) to 72.34 (15.48), and an increase in medication use was observed (53% to 63.2%). Corticosteroids were checked because this is a medicine that could affect atherosclerosis; hence, it could be a confounding factor for the risk of CVD.

CHANGE IN HEALTH PARAMETERS AND CARDIOVASCULAR RISK BETWEEN BASELINE AND FOLLOW-UP

Table 2 shows the health parameters and indicators of CVD risk of patients started on Cardiozym™ at baseline and at 6-month follow-up. When comparing health parameters between baseline and 6 months after Cardiozym™ intake, we found that there was a statistically significant decrease in TC, LDL, non-HDL, SBP and DBP. A small, significant increase in FBG was observed, while there was no significant change in TG and HbA1C levels. Only 16 patients had records of their HbA1C, so this was reported before and after the initiation of Cardiozym™. Regarding CVD risk parameters, there were significant reductions in both FRS and 10-year CVD risk between baseline and follow-up.

The relationship between changes in health (lipid profile, FBG, HbA1C levels and BP measurements) and cardiovascular disease risk parameters after 6 months of Cardiozym™ use and age, sex, weight, smoking, and alcohol consumption is shown in Table 3. Significant associations were found between alcohol consumption and change in mean LDL levels (coefficient = -56.68, 95% CI: -99.46 to -13.90, p = 0.011) and change in mean TG (coefficient = -18.88, 95% CI: -4.46 to -33.20, p = 0.012). No significant associations were found between changes in the other health parameters, including both FRS and 10-year CV risk, and any of the independent variables studied.

The linear mixed models adjusted for age, sex, weight, and antihypertensive medication use showed statistically significant reductions in mean TC (coefficient = -40.3, 95% CI: -49.7 to -31.1, p < 0.001) and LDL (coefficient = -38.3, 95% CI: -47.1 to -29.5, p < 0.001) between baseline and follow-up visits. In addition, significant reductions in mean SBP (coefficient = -1.98, 95% CI: -2.93 to -1.03, p < 0.001), mean FRS (coefficient = -1.79, 95% CI: -2.73 to -0.85, p < 0.001), and 10-year cardiovascular risk (coefficient = -1.89, 95% CI: -2.96 to -0.81, p < 0.001) were observed between the two visits.

The linear mixed models adjusted for age, sex, weight, and the use of antihypertensive drugs, showed statistically significant reductions in mean cholesterol levels (coefficient = -40.3, p < 0.001, 95% CI: -49.7 to -31.1) and LDL levels (coefficient = -38.3 p < 0.001, 95% CI: -47.1 to -29.5), and mean SBP (coefficient = -1.98, p < 0.001, 95% CI: -2.93 to -1.03), between the initial visit and the follow-up visit (Table 4).

CHANGE IN CARDIOVASCULAR RISK BETWEEN BASELINE AND FOLLOW-UP

At baseline, the average FRS was 11.87 ± 5.37. Based on the FRS, the predicted 10-year CV risk was found to be 4.74 ± 5.82. Overall, 86.8%, 10.5%, and 2.6% of patients initiated on Cardiozym™ were at low, intermediate, and high risk of CVD according to FRS categorization. Following the 6-month administration of Cardiozym™, there was a significant overall decrease in both FRS (p<0.001) and 10-year CV risk (p<0.001), as shown in Table 2.

After adjusting for age, gender, weight, smoking and alcohol consumption, no significant associations were found between changes in both FRS and 10-year CV risk and any of the variables. However, adjusting for age, gender, weight, and the administration of antihypertensive medications in the linear mixed models' analysis, significant reductions in mean FRS (coefficient = -1.79, $p < 0.001$, 95% CI: -2.73 to -0.85) and 10-year CV risk estimates (coefficient = -1.89, $p < 0.001$, 95% CI: -2.96 to -0.81) were observed between the two visits (Table 4).

DISCUSSION

In the present study, in patients at risk for CVD, we showed that 6 months of Cardiozym™ treatment significantly reduced TC, LDL, and non-HDL levels. The study also showed a statistically significant reduction in both SBP and DBP. In addition to these improvements in various health parameters, significant reductions from baseline to follow-up were observed in mean FRS and consequently in 10-year CV risk.

While numerous previous studies have demonstrated the lipid-lowering effects of RYR,[15-17] HT,[10,18] and CoQ10[9,19-21] in monotherapy, only a limited number of studies have examined their synergistic effects. In this regard, our results contributed to this field by demonstrating their combined effect on the reduction of TC, LDL, and non-HDL levels, similar to the results of other studies.[22-23]

Our study reported a statistically significant decrease in both SBP and DBP over the 6-month supplementation period, even after adjustment for antihypertensive medication. However, in literature, the effects of combinations of RYR, HT, or CoQ10 on BP were variable. While data from one study[13] reported a similar trend, indicating that RYR and CoQ10 co-therapy led to a significant reduction in BP, another recent systematic review and meta-analysis showed no beneficial effects of a similar combination on BP.[14] These discrepancies may be due to differences in patient characteristics such as medical conditions, different formulations used, intervention protocol and duration, as well as assessment methods and study designs.

In terms of CVD risk reduction, our results are comparable to those of studies of RYR, CoQ10, or HT as monotherapy, showing a reduction in CV risk. According to some studies, RYR formulations were effective in reducing metabolic syndrome risk and preventing CVD.[24,25] Others showed that CoQ10 supplementation reduced CVD risk in diabetic patients by lowering CVD risk-related indices such as TC and LDL.[21] Notably, none of these studies examined the synergistic effects of the components of Cardiozym™ or assessed CVD risk using the FRS, as in our study. Therefore, direct comparisons with the results of our study are challenging. Overall, by shedding light on the effects of these components, our study highlights Cardiozym™ as an intervention with promising implications for CV health management. It is important to note that while these results are encouraging, the relatively limited number of studies investigating the synergistic effects of HT, CoQ10, and RYR combinations on CV risk underscores the need for further research, ideally including controlled trials with longer follow-up, to validate and refine our findings.

STRENGTHS AND LIMITATIONS

The novelty of our study was to investigate the synergistic effects of RYR, HT and CoQ10 administered in a single formulation to modulate lipid levels, BP, and CV risk. The use of the well-established FRS provides a quantitative measure of CV risk, increases the accuracy and consistency of the measurements, and strengthens the validity of our results. In addition, a wide range of health parameters, including lipid profiles, blood pressure and FRS, were systematically evaluated, providing a comprehensive overview of the impact of Cardiozym™ on CV health.

However, several limitations of the study should be noted, including the observational nature of its design. Data were collected from patients' medical records, which did not allow

for an assessment of patient adherence to the prescribed dose of the supplement, in addition to the relatively small sample size, which may limit the generalizability of the findings. Another limitation was that patients' lifestyle modifications could have contributed to the positive outcomes. Future clinical trials with control groups, longer follow-up, and larger sample sizes are essential to extend our findings.

CONCLUSION

To our knowledge, this is the first study to evaluate the real-world use of Cardiozym™ in patients at risk for CVD. While our findings contribute to the existing body of knowledge on the effects of RYR and monacolin K, CoQ10 and HT on lipid profile, they provide valuable insights into the synergistic beneficial effects of this combination on CVD risk. Further comprehensive studies, ideally including controlled trials with longer follow-up, are essential to validate and refine our findings and ultimately contribute to a more holistic understanding of the role of Cardiozym™ in improving CV outcomes.

ABBREVIATIONS

BP: Blood Pressure
CI: Confidence Interval
CKD: Chronic Kidney Disease
CoQ10: Co-enzyme Q10
CV: Cardiovascular
CVD: Cardiovascular Disease
DBP: Diastolic Blood Pressure
CRF: Case Report Form
FBG: Fasting Blood Glucose
FRS: Framingham Risk Score
HDL: High-Density Lipoprotein
HT: Hydroxytyrosol
IRB: Institutional Review Board
LDL: Low-Density Lipoprotein
MI: Myocardial Infarction
RYR: Red Yeast Rice
SBP: Systolic Blood Pressure
SD: Standard Deviation
TC: Total Cholesterol
TG: Triglycerides

REFERENCES

1. Harris RE. Epidemiology of Chronic Disease: Global Perspectives. Jones & Bartlett Learning; 2019.
2. Mensah GA, Wei GS, Sorlie PD, et al. Decline in Cardiovascular Mortality: Possible Causes and Implications. Circ Res 2017;120:366–80.
3. Jenkins DJA, Spence JD, Giovannucci EL, et al. Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment: JACC Focus Seminar. J Am Coll Cardiol 2021;77(4):423-436.
4. Ingles DP, Cruz Rodriguez JB, Garcia H. Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment. Curr Cardiol Rep 2020;22:22.
5. Cicero AFG, Fogacci F, Stoian AP, et al. Red Yeast Rice for the Improvement of Lipid Profiles in Mild-to-Moderate Hypercholesterolemia: A Narrative Review. Nutrients 2023;15:2288.
6. Rabanal-Ruiz Y, Llanos-González E, Alcain FJ. The Use of Coenzyme Q10 in Cardiovascular Diseases. Antioxidants 2021;10:755.
7. Mantle D. Coenzyme Q10 and cardiovascular disease: an overview. Br J Cardiol 2015;22:160.
8. Gutierrez-Mariscal FM, de la Cruz-Ares S, Torres-Peña JD, et al. Coenzyme Q10 and Cardiovascular Diseases. Antioxidants 2021;10:906.
9. Jorat MV, Tabrizi R, Mirhosseini N, et al. The effects of coenzyme Q10 supplementation on lipid profiles among patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. Lipids Health Dis 2018;17:230.
10. Noguera-Navarro C, Montoro-García S, Orenes-Piñero E. Hydroxytyrosol: Its role in the prevention of cardiovascular diseases. Heliyon 2023;9:e12963.
11. D'Angelo C, Franceschelli S, Quiles JL, et al. Wide Biological Role of Hydroxytyrosol: Possible Therapeutic and Preventive Properties in Cardiovascular Diseases. Cells 2020;9:1932.
12. D'Addato S, Scandiani L, Mombelli G, et al. Effect of a food supplement containing berberine, monacolin K, hydroxytyrosol and coenzyme Q10 on lipid levels: a randomized, double-blind, placebo-controlled study. Drug Des Devel Ther 2017;11:1585–92.
13. Mazza A, Lenti S, Schiavon L, et al. Effect of Monacolin K and COQ10 supplementation in hypertensive and hypercholesterolemic subjects with metabolic syndrome. Biomed Pharmacother Biomedecine Pharmacother 2018;105:992–6.
14. Cicero AFG, Kennedy C, Knežević T, et al. Efficacy and Safety of Armolipid Plus®: An Updated PRISMA Compliant Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials. Nutrients 2021;13:638.
15. Tavan A, Noroozi S, Zamiri B, et al. Evaluation the effects of red yeast rice in combination with statin on lipid profile and inflammatory indices; a randomized clinical trial. BMC Nutr 2022;8:138.
16. Rahmani P, Melekoglu E, Tavakoli S, et al. Impact of red yeast rice supplementation on lipid profile: a systematic review and meta-analysis of randomized-controlled trials. Expert Rev Clin Pharmacol 2023;16:73–81.
17. Cicero AFG, Fogacci F, Stoian AP, et al. Red Yeast Rice for the Improvement of Lipid Profiles in Mild-to-Moderate Hypercholesterolemia: A Narrative Review. Nutrients 2023;15:2288.
18. Peyrol J, Riva C, Amiot MJ. Hydroxytyrosol in the Prevention of the Metabolic Syndrome and Related Disorders. Nutrients 2017;9:306.
19. Ardekani A, Tabrizi R, Maleki E, et al. Effects of coenzyme Q10 supplementation on lipid profiles and liver enzymes of nonalcoholic fatty liver disease (NAFLD) patients: A systematic review and meta-analysis of randomized controlled trials. Food Sci Nutr 2023;11:2580–8.
20. Liu Z, Tian Z, Zhao D, et al. Effects of Coenzyme Q10 Supplementation on Lipid Profiles in Adults: A Meta-analysis of Randomized Controlled Trials. J Clin Endocrinol Metab 2022;108:232–49.
21. Dludla PV, Nyambuya TM, Orlando P, et al. The impact of coenzyme Q10 on metabolic and cardiovascular disease profiles in diabetic patients: A systematic review and meta-analysis of randomized controlled trials. Endocrinol Diabetes Metab 2020;3:e00118.
22. Tshongo Muhindo C, Ahn SA, Rousseau MF, et al. Efficacy and safety of a combination of red yeast rice and olive extract in hypercholesterolemic patients with and without statin-associated myalgia. Complement Ther Med 2017;35:140–4.
23. Verhoeven V, Van der Auwera A, Van Gaal L, et al. Can red yeast rice and olive extract improve lipid profile and cardiovascular risk in metabolic syndrome?: A double blind, placebo controlled randomized trial. BMC Complement Altern Med 2015;15:52.
24. Yuan R, Yuan Y, Wang L, et al. Red Yeast Rice Preparations Reduce Mortality, Major Cardiovascular Adverse Events, and Risk Factors for Metabolic Syndrome: A Systematic Review and Meta-analysis. Front Pharmacol 2022;13:744928.
25. Verhoeven V, Lopez Hartmann M, Remmen R, et al. Red yeast rice lowers cholesterol in physicians - a double blind, placebo controlled randomized trial. BMC Complement Altern Med 2013;13:178.

Table 1. Baseline characteristics of patients initiated on Cardiozym™ (n=38).

	Baseline	Follow-up
	Mean (SD)	Mean (SD)
Age (years)	50.60 (11.38)	
Height (cm)	164.18 (8.52)	
Weight (kg)	75.90 (12.13)	72.34 (15.48)
	n (%)	n (%)
Sex		
Female	24 (63.0)	
Male	14 (37.0)	
Menopause	17 (71.0)	
Hormone replacement therapy	1 (6.0)	
Medication intake	19 (53.0)	24(63.2)
Antihypertensives	8 (21.1)	
Corticosteroids	0 (0.0)	
Smoking	4 (10.5)	4 (10.5)
Alcohol consumption	4 (10.5)	4 (10.5)
Relevant medical history		
Cardiovascular disease	0 (0.0)	
Cancer	1 (2.6)	
Diabetes	1 (2.6)	
Renal	0 (0.0)	
Hypertension	8 (21.1)	
Chemotherapy in the past two years	0 (0.0)	
Family History of CVD	19 (50.0)	
Family history of sudden death	3 (7.9)	

CVD: Cardiovascular Disease, SD: Standard deviation. Values are expressed as frequency and percentage except for age, height, and weight that are given as means and standard deviations.

Table 2. Health parameters and cardiovascular risk of patients initiated on Cardiozym™ at baseline and 6-month follow-up.

	Baseline	Follow-up	P-value
Lipid Profile			
Total cholesterol (mg/dL)	241.6 ± 29.7	201.2 ± 33.5	<0.001
LDL (mg/dL)	160.3 ± 30.8	122.0 ± 31.3	<0.001
HDL (mg/dL)	56.8 ± 14.1	57.4 ± 11.7	0.65
Triglycerides (mg/dL)	147.8 ± 93.7	132.9 ± 66.6	0.17
Non-HDL (mg/dL)	176.7 ± 49.4	146.2 ± 31.5	0.026
Fasting Blood Sugar	5.24 ± 0.77	6.19 ± 4.24	0.02
HbA1C (n=16)	5.47 ± 0.52	5.47 ± 0.45	0.96
Blood Pressure			
Systolic Blood Pressure (mm Hg)	126.92 ± 13.52	123.36 ± 9.05	0.02
Diastolic Blood Pressure (mm Hg)	78.21 ± 9.34	75.21 ± 6.11	0.03
Framingham Risk Score (FRS)	11.87 ± 5.37	9.92 ± 4.49	<0.001
10-Year Cardiovascular Risk (%)	4.74 ± 5.82	2.78 ± 3.59	<0.001
Cardiovascular Risk Category			
Low risk	33 (86.8%)	35 (94.6%)	
Intermediate risk	4 (10.5%)	1 (2.70%)	
High risk	1 (2.6%)	1 (2.70%)	

LDL: Low-Density Lipoprotein Cholesterol, HDL: High-Density Lipoprotein Cholesterol, HbA1C: Glycated Hemoglobin. Summary statistics are expressed as mean ± standard deviation for continuous variables, and as frequency (%) for categorical variables.

Table 3. Linear regression models for the association between age, sex, weight, smoking, alcohol consumption and change in health and cardiovascular disease risk parameters between baseline and after 6 months of Cardiozym™ use in patients included in the study.

		Coefficient	Lower 95% CI	Upper 95% CI	P-value
LDL	Age	0.35	- 0.78	1.49	0.53
	Sex	10.38	-15.83	36.59	0.427
	Weight	0.28	-0.77	1.34	0.6
	Smoking	28.75	-17.19	74.7	0.212
	Alcohol	-56.68	-99.46	-13.9	0.011*
Triglycerides	Age	0.67	-0.55	1.89	0.271
	Sex	4.5	-23.41	32.41	0.745
	Weight	-0.69	-1.75	0.37	0.196
	Smoking	-18.94	-60.22	22.34	0.357
	Alcohol	-18.88	-4.46	-33.20	0.012*
Fasting blood glucose	Age	0.67	-0.55	1.89	0.271
	Sex	4.5	-23.41	32.41	0.745
	Weight	-0.69	-1.75	0.37	0.196
	Smoking	-18.94	-60.22	22.34	0.357
	Alcohol	-18.88	-60.16	22.4	0.358
SBP	Age	0.075	-0.34	0.187	0.564
	Sex	2.065	-4.009	8.14	0.495
	Weight	-0.11	-0.36	0.13	0.36
	Smoking	3.97	-5.55	13.49	0.403
	Alcohol	8.16	-1.044	17.37	0.081
Framingham Risk Score	Age	-0.08	-0.16	0.008	0.075
	Sex	-1.45	-3.46	0.56	0.153
	Weight	0.019	-0.064	0.101	0.65
	Smoking	0.85	-2.37	4.06	0.59
	Alcohol	0.29	-2.94	3.52	0.858
10-Year Cardiovascular Risk	Age	-0.05	-0.15	0.053	0.340
	Sex	1.25	-1.076	3.58	0.283
	Weight	-0.028	-0.12	0.06	0.547
	Smoking	-0.99	-4.67	2.69	0.588
	Alcohol	1.25	-2.42	4.92	0.5

CI: Confidence interval; LDL: Low-Density Lipoprotein Cholesterol, SBP: Systolic Blood Pressure.
* A p-value <0.05 is considered statistically significant.

Table 4. Linear mixed models for the change in health and cardiovascular disease risk parameters between baseline and after 6 months of Cardiozym™ use in patients included in the study.

	Coefficient	Lower 95% CI	Upper 95% CI	P-value*
Total Cholesterol	-40.3	-49.7	-31.1	<0.001
LDL	-38.3	-47.1	-29.5	<0.01
SBP	-1.98	-2.93	-1.03	<0.001
Framingham Risk Score	-1.79	-2.73	-0.85	<0.001
10-Year Cardiovascular risk	-1.89	-2.96	0.81	0.001

CI: Confidence Interval; LDL: Low-Density Lipoprotein Cholesterol, SBP: Systolic Blood Pressure.
* A p-value <0.05 is considered statistically significant.

KIRBY CUTAJAR, TERRENCE MIFSUD

Speech and Language Success:

Early Intervention for Lasting Impact

ABSTRACT

Early intervention is essential for addressing potential communication disorders, with speech-language pathologists playing a pivotal role in diagnosis, assessment and treatment. Beyond their traditional duties, speech-language pathologists also work collaboratively with healthcare and medical professionals to identify early clinical markers, ensuring timely referrals and intervention. This article explores the role of speech-language pathologists in early intervention, particularly within the multilingual context of Malta, and provides medical professionals with guidance on identifying risk markers by underlining the main developmental milestones. Through the identification of these markers, practitioners may proactively foster early intervention and improve outcomes for youngsters at risk of speech and language difficulties.

KEYWORDS

Early Intervention, Speech-Language Therapy, Language Milestones, Prevention

This article is lovingly dedicated to the memory of Ms Leanne Schembri whose kindness, dedication and commitment left a lasting impact on us all. Her invaluable support towards the Association of Speech and Language Pathologists and her contributions towards this article will always be remembered.

INTRODUCTION

The implementation of early intervention (EI) assists in mitigating the manifestations of disabilities, difficulties, or disorders in young children. This is done by detecting possible deficits in the five main developmental areas: cognitive, communication, physical, social-emotional, and adaptive development.[1] EI is an approach that incorporates indispensable strategies utilised by various professionals and guardians to elevate the infant/toddler's developmental trajectory between the ages of 0 and five.[2]

ROLE OF THE SPEECH-LANGUAGE PATHOLOGISTS

Speech-Language Pathologists (SLPs) have an indispensable role in EI. SLPs are health-allied professionals who work with children and adults to prevent, assess, diagnose, and address issues related to speech, language, social communication, cognitive-communication, and swallowing.[3] SLPs operate under an **open referral system**, meaning that any agency or entity (even the clients themselves) can contact SLPs for a consultation. Clients may also be referred to the Speech and Language Therapy service by other medical professionals and caregivers.

The medical practitioner in question must consider both internal and external variables that arise due to Malta's bilingual context, whilst considering therapy targeting early intervention. For example, some studies have highlighted the increased frequency of phonological error patterns among multilingual children.[4]

On the other hand, the results of research by Grech & Dodd (2008) suggest that learning a language in a bilingual setting could boost phonological acquisition. In keeping with the latter, children who were exposed to both Maltese and English at home seemed to have an edge in terms of consistency and the percentage of correct consonants (PCC).[5]

PREVENTION OF COMMUNICATION DIFFICULTIES

Initiatives aimed at prevention have been shown to be effective in minimising the prevalence of communication difficulties, including hearing loss. Moreover, prevention is more economical than other rehabilitation costs.[6] There are three stages to identifying and preventing problems in human communication: primary, secondary, and tertiary.

Primary prevention incorporates the prevention of disease and the promotion of health. It focuses on the prevention of disorders and promotion of overall health through early identification and intervention. By altering susceptibility or lowering the exposure of susceptible people to risk factors, communication-based primary preventive programs can halt the progression of a communication problem. While not all conditions/difficulties may be prevented, their characteristics can be minimised through appropriate secondary preventative measures. Medical practitioners and paediatricians have a crucial role in primary prevention by supporting families who are concerned about the development of their children. An awareness of language and communication milestones, which are discussed further in this article, may guide medical professionals when outlining risk factors and the possible need for intervention. The goal of secondary prevention is to provide early communicative intervention in addition to early detection of impairments and issues. Therapy and early detection may be able to lessen the severity of its consequences or postpone its progression. Secondary preventative measures include screenings for language deficits and hearing impairments. In Malta, the national screening program 'Lenti fuq l-Iżvilupp ta` Wliedna' is an efficacious tool to assess the possible presence of autism spectrum disorder (ASD) in toddlers through the M-CHAT questionnaire.[7] This screening is performed at 24 months in Health centres and administered by an SLP. Moreover, tertiary prevention is aimed at mitigating the impact of an impairment by striving to restore typical functioning. The primary strategy in Speech and Language Therapy is to rehabilitate the individual with a communication impairment in order to address not only the primary disorder but also any secondary deficits that may have developed as a consequence. By treating the primary difficulty early and effectively, secondary complications such as social withdrawal, academic difficulties or behavioural issues can be minimised or avoided altogether. Tertiary prevention might include education programs for families and carers, client counselling, and interdisciplinary guidance.

Literature reports that the most intensive period for acquiring speech and language skills is during the first three years of life. While children vary in their development of both speech and language skills, a natural progression or timetable for the mastering of such skills exists. Language milestones may support professionals in monitoring the child's development whilst making considerations for further referrals as deemed necessary. Language difficulties may be caused by hearing loss, while at other times they are due to a speech and language disorder.[8] Otitis media is also a common cause of language difficulties, which is most highly prevalent between the ages of 6 and 24 months. This may adversely impact language development and further underlines the importance of early detection through a systematic screening tool.[9]

SPEECH-LANGUAGE PATHOLOGISTS OPERATE UNDER AN OPEN REFERRAL SYSTEM, MEANING THAT ANY AGENCY OR ENTITY (EVEN THE CLIENTS THEMSELVES) CAN CONTACT SPEECH-LANGUAGE PATHOLOGISTS FOR A CONSULTATION

LANGUAGE MILESTONES

A screening is usually a checklist or an observation form compiled by the medical professional, addressing a child's natural speech and language milestones. If a child 'fails' the screening, a prompt referral for a complete speech and language examination by an SLP may be opted for. Following this, an intervention strategy is developed and, if necessary, offered.[10]

The tables below comprise a checklist outlining important speech, language, social communication, and play milestones that may provide the possibility of tracking the child's overall development. This checklist was adapted from reliable sources online, which are referenced in the reference list.[11-27]

STAGES OF LANGUAGE DEVELOPMENT CHECKLIST

LANGUAGE COMPREHENSION

Months	Language comprehension
0 - 6	Responds to adult tones and intonations
6 - 12	Situational understanding emerges (Eg. Saying 'bye bye' and the child waves) Understands basic nouns Responds to his/her name
12 - 18	Understands further vocabulary Understands familiar phrases Understands simple instructions
19 - 24	Understands about 300 words
25 - 30	Understands around 500 words Answers simple questions such as: 'where is the ball?', 'what is this?'
	Follows directions such as: 'Get your shoes and socks'
31 - 36	Understands: • pronouns • adjectives • action words • prepositions • WH questions (What, who, where, why) • gender • understands 3-word sentences
37 - 48	Understands over 3000 words
49 - 60	Understands abstract concepts and ideas

LANGUAGE EXPRESSION

Months	Language expression
0 - 6	Coughs, cries and sucks to communicate Coos (6-8 weeks) Imitates basic sounds (Vocal play)
6 - 12	Babbles sounds Imitates sounds
12 - 18	Says around 20 single words Imitates adult verbal expression
19 - 24	Uses at least 50 different words Uses environmental sounds 'vroom vroom', 'beep beep' Uses pronouns Uses possessives Asks for help
25 - 30	Uses around 200 words Combines two or more words together Uses prepositions Verbalises actions
	Uses descriptive words Refers to the self by name Names different body parts Repeats parts of conversations Uses words reflecting self-centeredness
31 - 36	Uses phrases such as 'look at me!' Says his/her name when asked Plural words start to emerge Asks 'why?' and 'how?' Applies suffixes to verbs: '-ing', '-ed' Understood more clearly by listeners Uses verbal requests 900-1000 words by age 3
37 - 48	Speaks in 4 or more words Talks about daily activities Asks and answers yes vs no questions
49 - 60	Uses complex sentences Uses words such as 'and' and 'because'

SOCIAL COMMUNICATION AND PLAY SKILLS

Months	Social communication and play skills
0-6	Maintains eye contact (for few seconds) Laughing during play Socially smiles when approached Cries frequently Engages in unoccupied play
6 - 12	Engages in peek-a-boo Lifts arms towards the parent Responds to facial expressions Extends toys to others Imitates adult actions Engages in solitary play
12 - 18	Makes simple requests Attempts to protest Comments Shows objects to caregivers Points and vocalises Solicits attention vocally Uses 'bye'
	Uses gestures and verbal language together Maintains longer eye contact Sympathy and empathy are demonstrated Solitary play is observed
19- 24	Engages in turn taking Demonstrates simple topic control Expresses intention socially Onlooker play - observes other children
25 - 30	Expresses emotions Uses attention-getting words Clarifies/asks for clarification Initiates parallel play

Months	Social communication and play skills
31 - 36	Names/ points to self in photos Engages in nursery rhymes Starts to form bonds with close peers Engages in associative play
37-48	Increase use of symbolic play Negotiates with others Enjoys structured activities Emergence of cooperative play
49 - 60	Engages in further cooperative play Group activities are enjoyed by the child Understands the concept of teamwork

CONCLUSION

In conclusion, early intervention ensures a more positive prognosis for children who are exhibiting signs of speech, language and communication disorders. Long-term prospects are improved when addressing possible difficulties at an early stage. Advocating for early intervention programs is imperative as it empowers individuals to reach their full potential.

ADDITIONAL READING RESOURCES

American Speech-Language-Hearing Association. Communication milestones. www.asha.org/public/developmental-milestones/communication-milestones/

Sharma A, Cockerill H, Sanctuary C. Mary Sheridan's from birth to five years: Children's developmental progress. 5th ed. Routledge. 2021.

https://aslpmalta.org/

REFERENCES

1. American Speech-Language-Hearing Association. Scope of practice in speech-language pathology. 2016. Available from: https://www.asha.org/policy/
2. Robbins AM. The SLP and Early Intervention with Infants and Toddlers with Hearing Loss. *ASHA Leader* 2009;*14*(4):16-19.
3. American Speech-Language-Hearing Association. Speech-Language Pathologists and Early Intervention. *ASHA Leader* 2008;8(15):19-30.
4. Holm A, Dodd B. Comparison of Cross-Language Generalisation Following Speech Therapy. *Folia Phoniatrica Et Logopaedica 2001;53*(3):166-172.
5. Grech H, Dodd B. Phonological acquisition in Malta: A bilingual language learning context. *The International Journal of Bilingualism : Cross-Disciplinary, Cross-Linguistic Studies of Language Behavior 2008;12*(3):155-171.
6. American Speech-Language-Hearing Association. Prevention of Communication Disorders. Available from: https://www.asha.org/policy/ps1988-00228/?srsltid=AfmBOopFHbWDCLZ8Xwv5Ie5E_7Yxtd3rZLexcLdBsJgdpRBDegZatykY
7. Education, Science and Technology. Lenti project. 2025. Available from: https://www.servizz.gov.mt/en/Pages/Education_-Science-and-Technology/Education-Services/Educational-Support-Services/WEB-04210/default.aspx?utm_source=chatgpt.com
8. National Institute on Deafness and Other Communication Disorders. *Speech and language development milestones.* 2022. Available from: https://www.nidcd.nih.gov/health/speech-and-language
9. Danishyar A, Ashurst JV. Acute Otitis Media. 2023 Apr 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.
10. Siu AL; US Preventive Services Task Force. Screening for Speech and Language Delay and Disorders in Children Aged 5 Years or Younger: US Preventive Services Task Force Recommendation Statement. Pediatrics. 2015 Aug;136(2):e474-81.
11. American Speech-Language-Hearing Association. *Communication milestones: 19 to 24 months.* Available from: https://www.asha.org/public/developmental-milestones/communication-milestones-19-to-24-months/#:~:text=Uses%20and%20understands%20at%20least,or%20dah%20for%20%E2%80%9Cdog.%E2%80%9D&text=Puts%20two%20or%20more%20words,more%20water%20or%20go%20outside.&text=Follows%20two%2Dstep%20directions%E2%80%94like,put%20it%20on%20the%20table.%E2%80%9D
12. American Speech-Language-Hearing Association. *Communication milestones: 2 to 3 years.* Available from: https://www.asha.org/public/developmental-milestones/communication-milestones-2-to-3-years/
13. Children's Minnesota. *Speech and language development: 18 to 24 months.* Available from: https://www.childrensmn.org/images/pdf/speech18to24.pdf
14. Children's Minnesota. *Speech and language development: 24 to 30 months.* Available from: https://www.childrensmn.org/images/pdf/speech24to30.pdf
15. Great Ormond Street Hospital. *Speech and language development: Birth to 12 months.* Available from: https://www.gosh.nhs.uk/conditions-and-treatments/procedures-and-treatments/speech-and-language-development-birth-12-months/#:~:text=Stage%202%20(6%2D12%20months)&text=By%20six%20to%20nine%20months,his%20or%20her%20own%20name.
16. Healthline. *Language milestones: 0 to 12 months.* Available from: https://www.healthline.com/health/baby/language-milestones-0-to-12-months
17. Dosman CF, Andrews D, Goulden KJ. Evidence-based milestone ages as a framework for developmental surveillance. Paediatr Child Health 2012;17(10):561-8.
18. Nebraska Early Development Network. *Developmental milestones: 31 through 36 months.* Available from: https://edn.ne.gov/cms/developmental-milestones-31-through-36-months
19. Raising Children Network. *Development tracker: 4-5 years.* Available from: https://raisingchildren.net.au/preschoolers/development/development-tracker/4-5-years
20. Raising Children Network. *Language development: 4-5 years.* Available from: https://raisingchildren.net.au/preschoolers/development/language-development/language-4-5-years#:~:text=they%20can%20use.-,Sentences%20and%20grammar%20in%20language%20development,use%20many%20different%20sentence%20types.
21. Raising Children Network. *Language development: 1-2 years.* Available from: https://raisingchildren.net.au/toddlers/development/language-development/language-1-2-years
22. Gayathri K, Subramanian S, Mohan S, et al. Effectiveness of early intervention on developmental milestones among early-term babies. *Fizjoterapia Polska* 2023;23:281-285.
23. Speech and Language UK. *Ages and stages: 12-18 months.* Available from: https://speechandlanguage.org.uk/help-for-families/ages-and-stages/12-18-months/#:~:text=Say%20up%20to%2020%20single,out%20what%20the%20words%20are.
24. St. Jude Children's Research Hospital. *Language development: 3 to 4 years.* Available from: https://together.stjude.org/en-us/for-families/early-childhood-development/language-development-3-to-4-years.html#:~:text=a%20child's%20age.-,Language%20milestones,your%20family%20can%20understand%20them
25. Toddler Talk. *Milestones for 36-month-olds.* Available from: https://toddlertalk.com/blog/milestones-for-36-month-olds#:~:text=They%20understand%20the%20words%20for,begin%20to%20introduce%20academic%20concepts.
26. Toddler Talk. *12-month milestones for speech and language.* Available from: https://toddlertalk.com/blog/12-month-milestones-for-speech-and-language#:~:text=Most%20children%20say%20their%20first,as%2050%20or%20more%20words.
27. NHS Great Ormond Street Hospital for Children. Speech and language development from birth to 12 months. 2025. Available from: https://www.gosh.nhs.uk/conditions-and-treatments/procedures-and-treatments/speech-and-language-development-birth-12-months/

PETRA SPITERI

Mindfulness:

How, and When to Start this Evidence-based Practice

Mindfulness is a buzzword that many have heard about, but is it all about meditation in fixed, uncomfortable poses? Can it be incorporated in the busy lifestyle most of us lead, and do you need the patience to sit still for long? In these few paragraphs, Petra Spiteri will delve into the origins of mindfulness and how we can start to practice it.

Mindfulness is **"the awareness that arises by paying attention on purpose to the present moment non-judgementally."**[1] Mindfulness-based interventions are being used, together with other approaches, in a range of mental health conditions including eating disorders, posttraumatic stress disorder, obsessive–compulsive disorder, anxiety, insomnia, and substance use.[2] Various psychotherapeutic treatments, such as dialectical behaviour therapy, acceptance and commitment therapy, and mindfulness-based cognitive therapy (MBCT), incorporate mindfulness.[3] MBCT uses conventional methods of cognitive behavioural therapy (CBT) combined with mindfulness meditation.[4,5] MBCT was originally designed specifically for depression, but subsequently, variants of it were developed for 'obsessive-compulsive disorder, disordered eating, addiction, traumatic brain injury, obesity, and bipolar disorder, among others.'[6] Initially, it was Jon Kabat-Zinn in the 1970s who was a trained molecular biologist working in a hospital in America who convinced the hospital authorities to try out the Buddhist practices, that he gained so much from, as a new program. Together with his colleagues he developed this program with contemporary vocabulary and no reference to religious or Eastern cultural traditions. His program was known as Mindfulness-Based Stress Reduction (MBSR), and various studies have shown its impact on helping people deal with chronic pain and psoriasis symptoms.

In 1992, three cognitive psychologists (Zindel Segal, Mark Williams, and John Teasdale) contacted Kabat-Zinn and his Stress Reduction Clinic and formulated the MBCT program based largely on MBSR. The MBCT program was felt to be needed at the time because depression was mainly being tackled with one-to-one CBT or maintenance of high doses of antidepressants, and both are relatively expensive. Not everyone is comfortable with antidepressants, and the limited availability of trained therapists for CBT was also a propeller for this group-based intervention to be further developed and studied. Research conducted by the three cognitive psychologists into the prevention of depression by CBT showed that CBT did not change the content of depressive ideation, but it transformed the relationship of the client to the thoughts and feelings. The ensuing distancing and de-centering allows clients to see negativities as passing events rather than abiding realities. MBCT is now recommended as a front-line treatment in instances of relapsing depression by the UK National Health Service and is used by the United States Marine Corps for soldiers to maintain emotional awareness and resilience under pressure.[4,5] It is the author's opinion, based on published studies, that learning this practice should not be relegated to patients with the previously mentioned diagnosis but to anyone who wishes to enhance emotional awareness, and especially people with work that involves interaction with other people.

THE AWARENESS THAT ARISES BY PAYING ATTENTION ON PURPOSE TO THE PRESENT MOMENT NON-JUDGEMENTALLY

The mindful perspective may have an impact on therapeutic decisions and cooperation with patients, leading to better health effects.[7] An enhanced self-awareness in healthcare professionals and medical students, for example, can support them to reach out more frequently to self-care activities and to manage stress more effectively.[7]

Mindfulness involves opening to the here and now of all our subjective experiences without rigidly identifying with or resisting the experience. The formal practice of mindfulness is meditation, but there is also support in such courses to incorporate mindfulness into our daily life activities. One must note, however, that mindfulness sessions without any sensitivity to the presence of trauma has been shown to possibly generate problems for people struggling with traumatic stress. Being in a practice of sustained attention to our inner world can place us in contact with stimuli related to a traumatic event and can aggravate or intensify symptoms, or in some cases, lead to retraumatization.[8] Trauma is not only the conventional shock trauma medical professionals are used to. Trauma has also been seen as encompassing episodes where we are left feeling 'helpless, powerless, trapped, or lacking control.[9] With this definition, trauma can be bullying, a medical diagnosis of a loved one, discrimination, harassment, and childhood neglect. Hence, it is highly ethical for a mindfulness trainer to train in the provision of trauma-sensitive mindfulness to provide a training that can recognise the symptoms of trauma and adapt the practice to the needs of such clients.

So how can we start to practice mindfulness in a more trauma-sensitive way? Start by using the informal practice. Eating, showering, washing dishes, and walking can all be mindfulness practices. We take the time to smell, see colours, taste, touch as applies to the situation, and this moves us out of our busy minds and into the now. Then, when it comes to meditation, the regularity is important, but even a few minutes daily are supportive. With this meditation, the structure and function of the brain change to more emotional awareness, due to neuroplasticity.[10] A trauma-sensitive trainer will provide guidance on how to make this practice easy and adapted to suit one's needs.

REFERENCES

1. Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. Gen Hosp Psychiatry 1982;4(1):33-47.
2. Goldberg SB, Tucker RP, Greene PA, et al. Mindfulness-based interventions for psychiatric disorders: A systematic review and meta-analysis. Clin Psychol Rev. 2018;59:52-60.
3. Bruce N, Shapiro SL, Constantino MJ, et al. Psychotherapist mindfulness and the psychotherapy process. Psychotherapy (Chic). 2010;47(1):83-97. Erratum in: Psychotherapy (Chic). 2010;47(2):168.
4. Zhang T, Wang L, Bai Y, et al. Mindfulness-Based Cognitive Therapy in Major Depressive Disorder: A Study Protocol of a Randomized Control Trial and a Case-Control Study With Electroencephalogram. Front Psychiatry 2021;12:499633.
5. Zhang Z, Zhang L, Zhang G, et al. The effect of CBT and its modifications for relapse prevention in major depressive disorder: a systematic review and meta-analysis. BMC Psychiatry 2018;18(1):50.
6. Chaskalson M. Mindfulness in eight weeks. London: Harper Thorsons. 2014.
7. Chmielewski J, Łoś K, Łuczyński W. Mindfulness in healthcare professionals and medical education. Int J Occup Med Environ Health. 2021;34(1):1-14.
8. Treleaven DA. *Trauma-Sensitive Mindfulness. Practices for Safe and Transformative Healing.* New York: W.W. Norton & Company. 2018.
9. Stanley E. *Widen the Window.* Yellow Kite. 2021.
10. Calderone A, Latella D, Impellizzeri F, et al. Neurobiological Changes Induced by Mindfulness and Meditation: A Systematic Review. *Biomedicines* 2024; 12(11):2613.

DR CARLA GAUCI, DR SARAH ZRINZO, DR MURIEL BELLIZZI

Sacroiliac Joint Syndrome

A Multidisciplinary Perspective on Diagnosis and Management

Sacroiliac joint (SIJ) syndrome is characterized by pain originating from the sacroiliac joint due to degeneration or altered mobility. The SIJ has been implicated as the main source of pain in 10 - 26% of cases with this suspected pathology. With proper recognition and management, the impact of this condition on patients' lives can be significantly alleviated.

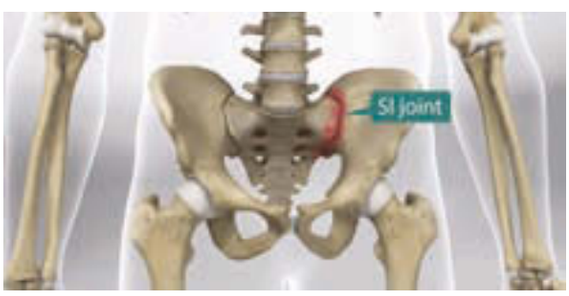
ANATOMY AND FUNCTION

The sacroiliac joint is a unique, weight-bearing synovial kidney shaped joint connecting the sacrum to the pelvis. Its stability relies on a network of ligaments and surrounding muscles, including the gluteus maximus and piriformis. Its anterior aspect is lined by an articular capsule, whilst its posterior aspect is covered by the interosseous sacroiliac ligament. Over time, degenerative changes and mechanical stress can compromise this balance, leading to pain.

The posterior portion of the joint is innervated from the lateral branches of L4-S3 dorsal rami. The innervation of the anterior SIJ is unclear.

While the joint permits slight movement, its primary role is to transfer load between the spine and lower limbs. It also allows slight mobility between the sacrum and ilium. It rotates in all three axes, although in very small movements. SIJs may be affected by changes in the lumbar spine, hips and symphysis pubis. 40 different muscles may influence the joint, although no muscles specifically move the joint.

Figure 1. The sacroiliac joint.



Degenerative changes which occur with time improve the stability of the joint but reduce the mobility. Ligaments maintain the stability of the joint until puberty, after which interlocking bone irregularities begin to form. By the eighth decade of life, the SIJ is locked in place secondary to fibrous degeneration, resulting in no movement of the joint.

PATHOPHYSIOLOGY AND PREDISPOSING FACTORS

SIJ syndrome can result from intra-articular conditions such as arthritis or infection, and extra-articular conditions like ligamentous injuries or fractures. Pathologies which may cause pain in the SIJ also include inflammation, infection, degeneration, trauma, metabolic changes and tumours.

Stretching that exceeds the joint's capacity can cause injury to the bone structure and ligaments. This may be secondary to weight-bearing or twisting movements.

There are various predisposing conditions associated with SIJ syndrome. A few of which include pregnancy, repetitive trauma, or postural abnormalities, which may all exacerbate joint dysfunction. During pregnancy, for instance, hormone-induced ligament laxity coupled with weight and gait changes often overloads the SIJ, leading to discomfort.

Lumbar spine surgery may also lead to additional stress on the SIJs.

DIAGNOSIS

Accurate diagnosis is challenging due to the similarity of symptoms with other conditions, such as lumbar facet joint arthritis or hip pathologies. In view of the complex sensory innervation of the SIJs, pain referral patterns may be highly variable.

Common presenting factors include localized pain to the ipsilateral buttocks (94%) or lower back (72%), often worsened by prolonged sitting, standing, or stair climbing. Other pain patterns include lower extremity, groin, upper lumbar region and abdominal pain.

SIJ syndrome is usually reproducible on physical examination when the joint is stretched. These physical tests include the FABER (Flexion, Abduction, External Rotation) and Gaenslen's tests, which are useful diagnostic tools.

Figure 2. FABER test: Reproduction of buttock pain suggests SIJ involvement.

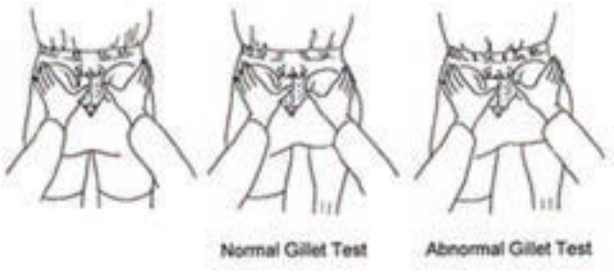
During the FABER test, pain is experienced in the buttock on the contralateral side of the flexed/ abducted limb if positive. On the other hand, back or ipsilateral groin pain a nonspecific sign which may indicate alternative pathology.

Figure 3. Gaenslen's test: Diagnostic manoeuvre stressing the SIJ.

In the Gaenslen's test, pain is felt in the affected SIJ (on the same side as the limb being passively extended) if positive.

Another diagnostic test which may be used is the Gillet test, during which the patient is asked to flex the affected limb at the knee.

Figure 4. Demonstration of the Gillet test.



During the Gillet test, the patient stands upright, bearing weight equally on both legs. The examiner places one thumb on the S2 spinous process and the other thumb on the posterior superior iliac spine. The patient then flexes the hip and knee of the tested leg, bringing the knee toward the chest. A positive test is demonstrated if the posterior superior iliac spine does not move downwards on the affected side. It suggests fixation of the SIJ on the tested side.

However, most of these diagnostic physical tests also cause stress on surrounding structures, which may be sources of pain. Therefore, do not isolate the SIJs.

No radiological features provide a definitive diagnosis, and around 25% of patients who are asymptomatic have positive radiological findings on X-Ray. Table 1 depicts the findings and the advantages and limitations present when using different modalities to help diagnose SIJ syndrome.

The gold standard remains a diagnostic injection of local anesthetic into the joint with alleviation of symptoms, although there is still a possibility of false positives (20%) or negatives.

Table 1. Radiological Modalities for Diagnosing Sacroiliac Joint Syndrome.

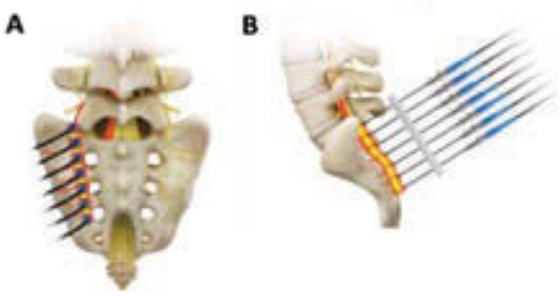
Radiological Modality	Findings	Advantages/Limitations
X-Ray	Used to assess fractures, joint space narrowing, or significant degenerative changes.	Lacks sensitivity for early inflammatory or subtle degenerative changes.
Computed Tomography (CT)	Provides detailed views of bony structures, detecting fractures, erosions, sclerosis, or ankylosis.	Superior resolution for bony details; does not visualize soft tissues or inflammation effectively.
Magnetic Resonance Imaging (MRI)	Preferred for detecting inflammation, soft tissue involvement, and edema. A STIR sequence is useful to highlight edema; a T1-weighted scan is useful to detect chronic anatomical changes.	Best for early inflammatory changes or soft tissue involvement, especially in spondyloarthropathies or infections.
Bone Scintigraphy (Bone Scan)	Detects increased metabolic activity, suggesting inflammation or pathological processes.	Useful for stress injuries or occult fractures; less commonly used.
Ultrasound	Evaluates soft tissues and guides injections.	Limited for SIJ visualization; non-invasive and real-time guidance.
Positron Emission Tomography (PET)	Detects increased metabolic activity in malignancies or infections.	Rarely used specifically for SIJ syndrome but helpful in complex cases.

The use of lumbar medial branch blocks and sacral lateral branch blocks has also been suggested for diagnostic use. However, in view of the variations in innervation and the possibility of local anaesthetic migration to other painful areas, this option is less attractive.

Injection into the SIJ may be challenging in itself. Extra-capsular spread is common. These infiltrations may be specifically challenging in the elderly in view of significant bony changes.

These infiltrations are performed under fluoroscopic or CT guidance. Blind injections have a poor success rate. It usually incorporates a steroid and a local anaesthetic as the treatment.

Figure 5. Schematic illustration of multiple needle placements and the location of the needles in both anteroposterior (A) and lateral views (B). The target nerves are L5 dorsal ramus and the lateral branches of the S1, S2, and S3 dorsal rami, which are the major innervating nerves of the posterior compartment of the sacroiliac joint.



MANAGEMENT STRATEGIES

Treatment begins with conservative approaches, including:

- **Physical Therapy:** An assessment should be carried out to identify clinically significant anatomical or functional abnormalities that may exacerbate SIJ dysfunction. While minor leg length discrepancies are common in the general population and usually asymptomatic, larger discrepancies (>1–2 cm) or functional imbalances may alter pelvic biomechanics and increase SIJ stress. Exercises to strengthen core and pelvic stabilizers can improve joint stability.
- **Pharmacotherapy**: Unless contraindicated, NSAIDs and adjunctive medications such as gabapentin, tricyclic antidepressants and SSRIs offer symptomatic relief.
- **Psychotherapy**
- **Support Devices:** Stabilization belts may reduce stress on hypermobile joints.

For refractory cases, **interventional techniques** are pivotal:

- **Intra-articular Injections**: A combination of local anaesthetics and steroids can provide diagnostic clarity and therapeutic benefit. These infiltrations have been proven to give short-term benefit. However, their long-term benefit has not been observed.
- **Radiofrequency Ablation (RFA):** This minimally invasive procedure targets the lateral branches of the dorsal sacral nerves, reducing pain by interrupting nerve signaling pathways. In a systematic review published in the journal *Current Pain and Headache Reports* in March 2024, findings indicated that RFA provides significant pain relief and functional improvement in patients with chronic SIJ pain.

The complicated and unpredictable anatomy of the innervation of the SIJ makes local anaesthetic and steroid infiltration a more attractive option.

Surgical intervention, such as SIJ fusion, is a last resort for severe cases unresponsive to other treatments.

CONCLUSION

SIJ syndrome underscores the complexity of chronic low back pain. By enhancing clinical awareness and adopting a multidisciplinary approach, healthcare providers can optimize patient outcomes, ensuring both relief from pain and restoration of function. As pain medicine evolves, integrating advanced diagnostics and therapies will further refine our capacity to address this prevalent condition.

This concise understanding of SIJ syndrome aims to aid practitioners in recognizing and managing this significant pain generator effectively.

BIBLIOGRAPHY

1. Cohen SP, Abdi S. Lateral Branch Blocks as a Treatment for Sacroiliac Joint Pain: A Pilot Study. *Reg Anesth Pain Med* 2003;28(2):113-119.
2. Aydin SM, Gharibo C, Mehnert M, et al. The Role of Radiofrequency Ablation for Sacroiliac Joint Pain: A Meta-Analysis. *PM&R* 2010;2(9):842-851.
3. Tasso M, Ugoccioni V, Bertolini N, et al. Role of Patrick-FABER test in detecting sacroiliitis and diagnosing spondyloarthritis in subjects with low back pain. *Clinical and Experimental Rheumatology* 2023;41(11):2298-2300.
4. Nejati P, Khadem-Rezaiyan M, Ameri E, et al. Accuracy of the Diagnostic Tests of Sacroiliac Joint Pain: A Systematic Review. *Archives of Bone and Joint Surgery* 2020;8(2):104-113.
5. Janapala RN, Knezevic E, Knezevic NN, et al. Systematic Review and Meta-Analysis of the Effectiveness of Radiofrequency Ablation of the Sacroiliac Joint. *Curr Pain Headache Rep* 2024;28(5):335-372.
6. Cheng J, Chen SL, Zimmerman N, et al. A New Radiofrequency Ablation Procedure to Treat Sacroiliac Joint Pain. *Pain Physician* 2016;19(8):603-615.

DR JESSICA MUSCAT

The Ongoing Breast Screening Debate

Time to Clear the Air

In an age of social media and digital algorithms, being able to empower patients with the correct information and facilitate the ability to make safe, informed decisions about healthcare is a role that healthcare providers cannot afford to underestimate. The merits of screening for Breast Cancer have been challenged by cynics for decades, but the evidence supports that more lives are saved when regular screening is employed.

HOW DOES SCREENING WORK?

Breast cancer screening aims to reduce breast cancer mortality by early detection and early treatment of asymptomatic cancer. In simple terms, picking things up early (by undergoing a screening examination) and, at a smaller size, gives the best possible outcome as there is an increased likelihood of the disease being contained, i.e. less chance of spread. Better systemic treatments have also contributed to the overall improved outcomes since the introduction of breast screening.

WHO TO SCREEN?

A risk factor is defined as anything that affects an individual's chance of developing a condition. Certain major risk factors for breast cancer are beyond an individual's control (Table 1). Simply being a woman is the main risk factor for breast cancer, with breast cancer being about 100 times more likely to occur in women than in men. Ageing also inevitably increases the risk of developing breast cancer. Almost 8 out of 10 women diagnosed are over the age of 50. Breast cancer is rare in people under 30 years (Table 2). Overall, 8% of women in the so-called developed world will get a breast cancer diagnosis by age 75 years.[1,2]

HOW TO SCREEN?

Studies show that even when women have access to the latest therapies, deaths from breast cancer decline at a much higher rate in women who get mammographic screening either in an organized programme or in the form of patient-initiated opportunistic screening.

In most European countries, mammographic screening programmes include all women, with age being the only determinant. Screening is offered starting at the age of 40–50 years until the age of 64–74 years at intervals of 1–2 years (3 years in the UK). A comparison of the different screening regimens shows that starting early at a regular shorter interval results in a higher reduction in mortality and more quality-of-life years gained (Table 3).[3]

Screening mammography is a standardised procedure composed of four projections,[2] two for each breast: the cranio-caudal projection and the medio-lateral oblique projection (Figure 1).

Despite the overall survival advantages achieved with the use of mammographic screening, this "one-size-fits-all" approach is associated with several drawbacks, not least that mammography alone is not sufficient to achieve early diagnosis in the high-risk population (Table 4).[4] Mammographic screening sensitivities of up to 89% in women with mainly fatty breasts drop to 62% in the case of women with dense breasts

due to the masking effect of glandular elements (Figure 2). Considering that about 40–50% of women have dense breasts (heterogeneously and extremely dense breasts), this represents a valid issue. Supplemental assessment, in practice, at least with ultrasonography, is recommended as an adjunct for further assessment of denser breasts.

LIMITATIONS OF BREAST SCREENING

Screening mammography involves exposure of the breast tissue to ionising radiation (which is potentially carcinogenic) in a presumed, and more likely than not, healthy population.

The effective dose for a standard 2-view mammogram of each breast is 0.4mSV for digital mammography. This may be comparable to 2 months of background radiation i.e. just being on the planet, quoted at 3mSV per annum or the equivalent of under a third of the effective dose from a lumbosacral spine X-ray. The small risk of radiation-induced cancer in an organised and controlled breast screening programme is outweighed by the benefits of expected mortality reduction.[5]

Cancer may still develop between one screening round and the next, known as an interval cancer. Any symptoms which develop in the interim should not be dismissed without a workup.

A number of screening clients may undergo additional tests, such as additional mammographic views or needle sampling, and associated worry, which result in a normal or benign diagnosis. The average risk of false positive recall of clients undergoing biennial screening aged 50-69 years has been calculated at 20%.[5]

Also, some screen-detected breast cancers would have never otherwise been found and would not have become life-threatening. This phenomenon is commonly known as overdiagnosis.

Overtreatment is, however, the real issue here. In truth, there is as yet no way to identify which breast cancers are not life-threatening, and treatment is offered for all diagnosed breast cancers.

SO, WHERE DOES THIS LEAVE US?

There should be no doubt that for the majority of our patients, breast screening - starting early and at a regular short interval - is better than the alternative. Early detection, essentially by imaging (4-view direct digital mammography +/- ultrasound) in conjunction with the improved systemic therapies available, saves lives.

Table 1. Risk factors of Breast Cancer.

Non-modifiable

- Age
- Gender
- Genetics (BRCA1/2)

Modifiable

- Hormonal factors
- Lifestyle
- Alcohol
- Obesity

Table 2. Age & Risk of Breast Cancer.

Risk up to and including age 29 years	1 in 2000
Risk up to and including age 39 years	1 in 315
Risk up to and including age 49 years	1 in 50
Risk up to and including age 59 years	1 in 22
Risk up to and including age 69 years	1 in 13
LIFETIME RISK	**1 in 8**

Table 3. Comparison of Screening Protocols.

SCREENING PROGRAMME	MORTALITY REDUCTION %	LIFE YEARS GAINED PER 1000 WOMEN SCREENED	MAXIMUM LIFETIME SCREENS PER WOMAN	NUMBER NEEDED TO SCREEN PER LIFE YEAR GAINED
No Screening	0.0	0.0	0	
Triennial ages 50-69	24.6	45.9	7	11.1
Triennial ages 50-74	27.9	50.8	9	9.4
Biennial ages 50-69	32.0	60.6	10	8.4
Biennial ages 50-74	36.2	66.8	13	7.2
Annual ages 40-49	18.6	37.1	10	17.2
Annual ages 50-69	45.6	85.6	20	5.9
Annual ages 50-74	49.5	92.5	25	5.2
Annual ages 40-49, Biennial ages 50-69	38.6	94.6	20	5.9
Annual ages 40-49, Biennial ages 50-74	40.9	101.3	22	5.5
Annual ages 40-69	49.8	118.8	30	4.5
Annual ages 40-74	53.0	124.9	35	4.1

Figure 1. The Mammogram. 4 VIEWS: Right & Left Mediolateral oblique views (a,b) and Bilateral Craniocaudal views (c,d).

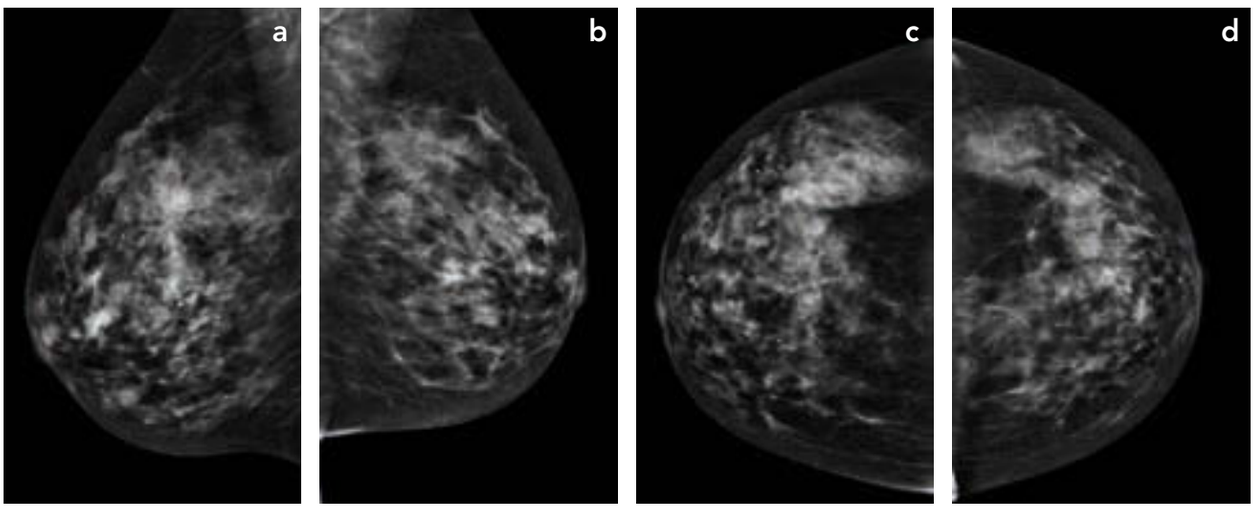
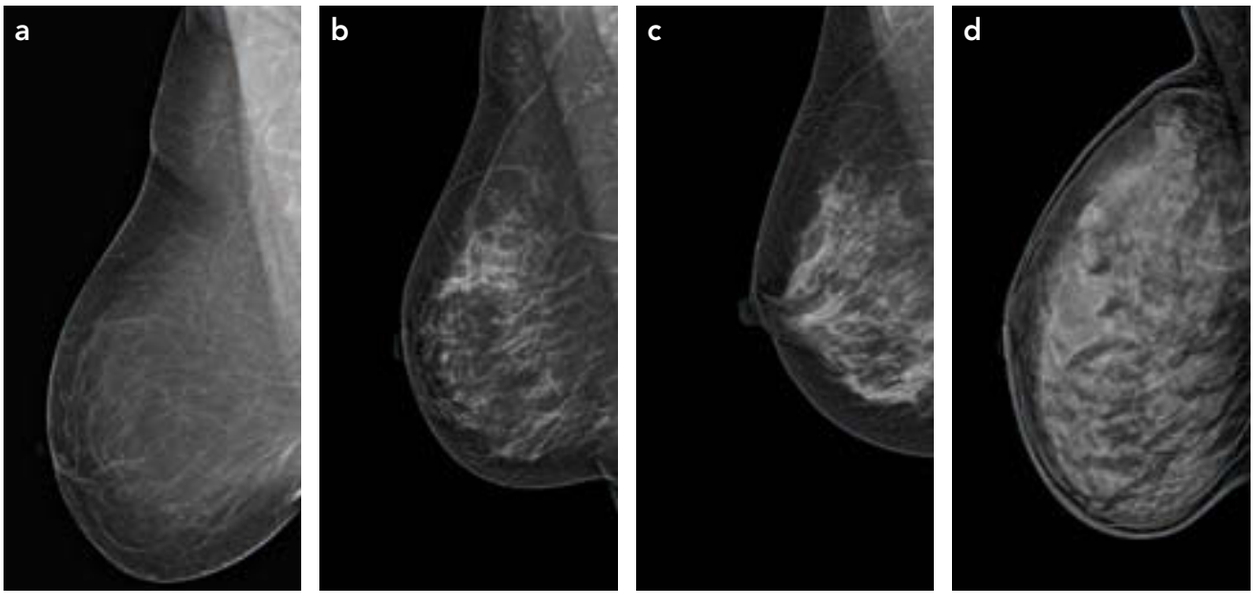


Table 4. High-Risk Breast Cancer – Breast MRI screening in these patients is recommended commencing at circa 30 years of age.

Pathogenic Variant	Lifetime risk of Breast Cancer
BRCA1	>60%
BRCA2	>60%
PALB2	40-60%
PTEN	40%
TP53	40%
CDH1	40% (Lobular breast cancer)
STK11	40%
ATM	25-30%
CHEK2	25-30%
BARD 1	20%
RAD51C	20%
RAD51D	10%

Figure 2. Breast density (proportion of fat to glandular elements in the breast) described as: a - Almost entirely fatty. b - Scattered fibroglandular tissue. c - Heterogenously dense. d - Extremely dense.



REFERENCES

1. Fallenberg EM, Fuchsjäger M [eds]. Screening & Beyond. Medical imaging in the Detection, Diagnosis and Management of Breast Diseases. European Society of Radiology. 2016. Available from:https://www.internationaldayofradiology.com/app/uploads/2017/09/IDoR-2016_Book-on-Breast-Imaging_Web_low.pdf
2. Sardanelli F, Fallenberg EM, Clauser P, et al. Mammography: an update of the EUSOBI recommendations on information for women. *Insights Imaging* 2017;8(1):11-18.
3. Yaffe MJ, Jong RA, Pritchard KI. Breast Cancer Screening: Beyond Mortality. *J Breast Imaging* 2019;1(3):161-165.
4. Wekking D, Porcu M, De Silva P, et al. Breast MRI: Clinical Indications, Recommendations, and Future Applications in Breast Cancer Diagnosis. *Current Oncology Reports* 2023;25:257-26
5. Pediconi F, Gilbert FJ [eds]. Breast Imaging. In: Modern Radiology eBook. European Society of Radiology. 2025. Available from: https://www.myesr.org/app/uploads/2025/05/ESR_Modern_eBook_11.pdf.

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CAREOMICS

X and Y Chromosome Typing in the Maltese Population: From Population Genetics to Clinical Practice

ABSTRACT

The CAREOMICS project is establishing a national framework for advanced genetic profiling in Malta that includes sex-chromosome markers. X-chromosomal Short Tandem Repeats (X-STRs) and Y-chromosomal STRs (Y-STRs) and Single Nucleotide Polymorphisms (Y-SNPs) are powerful tools in forensic casework, complex kinship analysis and population genetics. Although Maltese studies have characterised autosomal STRs, mitochondrial DNA and Y-chromosome variation, important gaps remain for sex-chromosome data in the local population. This review summarises the rationale for focusing CAREOMICS on X- and Y-chromosome typing, outlines key findings from previous Maltese Y-chromosome work, and describes the ongoing effort to generate the first systematic X-STR haplotype database for Malta. The clinical and forensic implications for healthcare professionals are discussed, particularly for kinship testing, missing-person identification and the interpretation of complex family structures in a small, historically rich island population.

INTRODUCTION: WHY SEX CHROMOSOMES MATTER IN CAREOMICS

The human sex chromosomes occupy a unique position within the genome: while autosomes recombine in both sexes, the Y chromosome is transmitted strictly along the paternal line, and its male-specific region (MSY) behaves largely as a non-recombining block that accumulates lineage-defining Y-SNPs and polymorphic Y-STRs passed from father to son, with occasional mutations generating new haplotypes. In contrast, the X chromosome recombines only in females; males inherit a single maternal X, whereas females inherit one X from each parent, producing characteristic patterns of linkage disequilibrium and haplotype structure that are highly informative in specific kinship scenarios. Within CAREOMICS (Comprehensive Approach for Rare Diseases Employing Multi-Omics Strategies), X- and Y-chromosome markers are viewed as complementary to autosomal STRs and mitochondrial DNA (mtDNA): Y-markers are particularly valuable for male-lineage reconstruction, paternal ancestry inference and the deconvolution of male components in mixed forensic samples, while X-markers, especially X-STRs arranged in linkage groups, enhance the resolution of complex kinship analyses involving daughters, paternal half-sisters and multi-generational pedigrees where autosomal data alone may be inconclusive. By integrating autosomal, X, Y and mtDNA markers in a coordinated project, CAREOMICS is laying the groundwork for a multi-layered genetic framework that reflects both the demographic history and clinical needs of the Maltese population.

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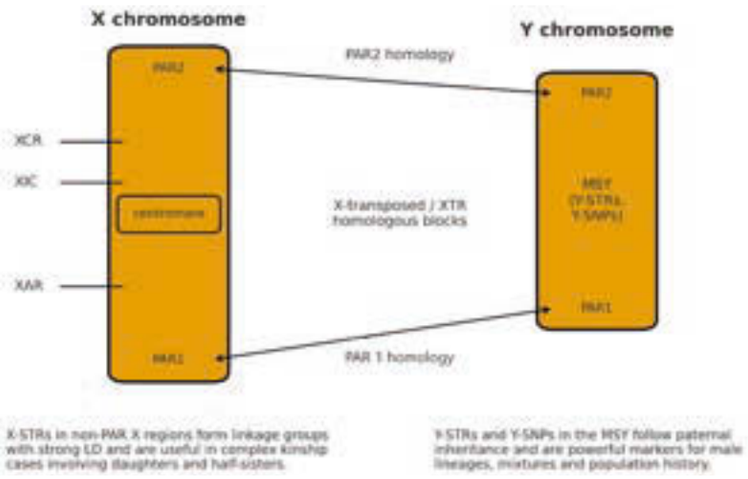
Figure 1. The homology and forensic regions of the sex chromosomes.

Visual representation of the human X and Y chromosomes, highlighting the homologous pseudoautosomal regions (PAR1 and PAR2), the X-transposed region, and chromosome-specific segments. The X chromosome is divided into the X-conserved region (XCR), X-inactivation centre (XIC), and X-added region (XAR), while the Y chromosome has the male-specific region (MSY) containing Y-STR and Y-SNP markers. PAR regions recombine between X and Y during male meiosis, whereas non-PAR regions are inherited in a sex-specific manner.



THE MALTESE Y CHROMOSOME: LESSONS FROM PAST AND ONGOING WORK

The paternal genetic history of Malta is relatively well studied and underpins the Y-chromosome arm of CAREOMICS: Capelli *et al.*, with Maltese participation by Professor Alex E. Felice, combined Y-SNPs and Y-STRs to place Maltese males within a Central–Eastern Mediterranean continuum, showing strong affinities to Sicily and Sardinia and identifying R1 and J2 as dominant haplogroups, reflecting mixed European and Near Eastern influences.[1] Cassar *et al.*, using autosomal STRs, confirmed close genetic similarity between Malta and Sicily, while Caruana's doctoral work, integrating mtDNA, Y-STRs and autosomal markers, highlighted the need for Malta-specific forensic databases rather than reliance on foreign allele frequency data.[2-3] Vella expanded Y-STR, Y-SNP and mtDNA datasets and contributed 292 Maltese Y-STR haplotypes to the Y Chromosome Haplotype Reference Database (YHRD),[4-5] a substantial resource but still below the ~400 samples recommended for a fully robust population database.

Overall, these studies show that the Maltese Y-chromosome landscape is neither isolated nor homogeneous. Instead, it reflects layered historical contacts with Sicily, North Africa and other Mediterranean ports. For forensic practice, male-lineage markers must therefore be interpreted against a locally informed background, where haplogroup frequencies and Y-STR diversity are specific to Malta. For CAREOMICS, this provides a baseline on which modern Y-typing using contemporary multiplex systems and high-resolution haplogrouping can be built.

Y-CHROMOSOME TYPING IN CAREOMICS

The Y-chromosome component of CAREOMICS, led by Daniel Brincat, is establishing a standardised, high-resolution Y-typing framework for forensic and research applications. Using the PowerPlex® Y23 System (PPY23), the analysis generates informative Y-STR haplotypes across 23 loci, well suited to a small yet genetically complex population such as Malta. In parallel, a qPCR–high-resolution melting (HRM) approach is applied to type key Y-SNPs and assign samples to major Y-haplogroups A–T and relevant subclades. Together, Y-STR haplotypes and Y-SNP haplogroups yield a two-layered dataset that improves Maltese haplogroup

frequency estimates, corrects earlier sampling biases, supports robust forensic and kinship analyses, and anchors local male lineages within a global phylogenetic framework

Practically, expanding and refining the Maltese Y-STR/Y-SNP database has immediate implications for healthcare and forensic professionals. Likelihood ratios for paternity testing, sexual offence investigations and missing-person identifications become more precise when calculated against population-specific data rather than imported references. Enriched Y-chromosome information will also enable future studies of male-specific disease susceptibilities and sex-biased demographic events in a small island population with known founder effects.

THE X CHROMOSOME: THE MISSING PIECE IN MALTESE FORENSIC GENETICS

The X chromosome remains a major gap in Maltese genetic databases, even though X-STRs are internationally recognised as key markers in forensic genetics and complex kinship testing, particularly in pedigrees involving at least one female (e.g. disputed paternity of daughters, paternal half-sisters, specific grandparent–grandchild cases), owing to their female-specific recombination and distinctive haplotype structure.[6] Studies in neighbouring Mediterranean populations highlight both the potential and complexity of these markers: Ferragut *et al*. used the Investigator® Argus X-12 kit to show subtle isolation and sex-biased gene flow in Valencia and the Balearic Islands, with Ibiza displaying low intra-population variability and strong linkage disequilibrium,[7] and broader Western Mediterranean work confirmed that X-STRs can differentiate groups with distinct migration and admixture histories while still detecting regional homogeneity.[8] Tomas and co-workers, combining X-STRs, X-SNPs and autosomal markers, demonstrated how X-linked data capture female-mediated migration and population structure not evident from autosomes alone,[9] while Robino and colleagues, focusing on Sardinia, showed how local isolation and drift can markedly shape X-STR haplotypes and linkage patterns, with important consequences for both population studies and forensic interpretation.[10-11]

Despite Malta's proximity to these populations, no dedicated X-STR database has yet been published for the Maltese population. As a result, forensic casework relying on X-linked markers, for example, in complex paternity disputes or half-sister testing, must currently use allele frequencies and haplotype patterns from other populations, often Sicilian, Italian or Iberian datasets. While broadly similar, the Maltese genetic landscape is not identical, and modest differences in allele frequencies can significantly alter likelihood ratios in borderline cases. From legal and ethical perspectives, being able to state that calculations are based on "Maltese data" rather than approximations represents a major advance.

BUILDING THE FIRST MALTESE X-STR DATABASE WITHIN CAREOMICS

The X-chromosome arm of CAREOMICS, led by Sarah Theuma, aims to generate the first population-level X-STR dataset for Malta, initially focusing on unrelated Maltese males, each carrying a single maternal X chromosome, which simplifies interpretation. Using multiplex kits such as GT XDetector (Genetek Biopharma) or the Investigator® Argus X-12 system, X-STR loci organised into four linkage groups are typed and treated as haplotypes rather than independent markers. The workflow follows standard forensic practice, DNA extraction, quantification, multiplex PCR and capillary electrophoresis, with alleles called and grouped into haplotypes (e.g. via GeneMarker® HID) and population-genetic analyses used to estimate allele/haplotype frequencies and diversity, with future female datasets enabling assessment of Hardy–Weinberg equilibrium and linkage disequilibrium within and between linkage groups.

Methodologically, the project is aligned with recommendations from the DNA Commission of the International Society for Forensic Genetics (ISFG) on X-chromosomal markers. Tillmar, Kling, and colleagues emphasise treating tightly linked X-STRs as haplotypes, accounting for linkage and linkage disequilibrium in likelihood calculations, and ensuring sufficiently large, well-characterised population datasets before casework use.[12] The CAREOMICS X-STR dataset is being designed with these principles in mind, targeting a sample size that balances practical constraints with statistical robustness.

Once established, the Maltese X-STR data will be compared to existing Mediterranean datasets, including those from Spain, the Balearic Islands, Sardinia, Greece and North Africa. This will allow Malta to be placed within the wider Mediterranean X-chromosome landscape, and to assess whether Maltese X-STR profiles are closer to those of neighbouring Sicily or show distinct patterns reflecting Malta's unique demographic history. Importantly, the dataset is intended to be formatted for integration into public or semi-public databases such as ChrX-STR.org and, where appropriate, for use within forensic software such as FamLinkX, which can perform likelihood computations for X-linked markers while accounting for linkage, recombination and mutation.

INTEGRATING X AND Y TYPING INTO A CAREOMICS FRAMEWORK

The X- and Y-chromosome projects form a unified CAREOMICS framework that integrates autosomal STRs, Y-STRs/Y-SNPs, X-STRs and mtDNA into population-specific databases and pipelines to support forensic practice and precision medicine in Malta. In casework, autosomal markers remain primary, with Y-STRs used to resolve male contributors and strengthen paternal lineages, and X-STRs boosting power in complex kinship analyses involving female relatives. More broadly, sex-chromosome data, combined with transcriptomic, epigenomic and metabolomic profiles, will enable studies of sex-biased disease, X-linked disorders and Y-related male health, while providing more accurate, locally grounded likelihood ratios that strengthen paternity and kinship testing, improve the robustness of court reports and align Maltese practice with international standards.

CONCLUSIONS

The CAREOMICS project is a major step toward a comprehensive, population-specific genetic framework for Malta, explicitly addressing two key gaps: limited resolution of existing Y-chromosome data and the previous absence of Maltese X-STR population data. Building on the work of Capelli, Vella, Cassar, Caruana and others, it applies modern multiplex kits, advanced analytical tools and ISFG-compliant guidelines to generate X- and Y-chromosome datasets that truly reflect the Maltese population.[1-5,12] For healthcare professionals and researchers, this will yield more precise and defensible genetic evidence in forensic and kinship cases, a stronger basis for multi-omics studies and a clearer view of Malta's place in the Mediterranean genetic landscape, making robust, locally derived sex-chromosome data a practical necessity rather than a luxury.

If interested in participating in this population genetics research, kindly contact Prof. Borg (joseph.j.borg@um.edu.mt).

REFERENCES

1. Capelli C, Redhead N, Romano V, et al. Population structure in the Mediterranean basin: a Y Chromosome Perspective. *Ann Hum Genet* 2006;70(2):207–25.
2. Cassar M, Farrugia C, Vidal C. Allele frequencies of 14 STR loci in the population of Malta. *Legal Med* 2008;10(3):153-56.
3. Caruana J. Population Genetics of Western Mediterranean Islands – Malta: a case study. Ph.D. Thesis. University of Manchester 2013.
4. Vella J. The Genetic Landscape of the Maltese and the Characterisation of Mitochondrial Disease. Ph.D. Thesis. University of Malta 2021.
5. YHRD. Contribution with Accession Number YA005722. Y Chromosome Haplotype Reference Database (Maltese dataset) 2021.
6. Pinto N, Gusmão L, Amorim A. X-chromosome markers in kinship testing: a generalisation of the IBD approach identifying situations where their contribution is crucial. *Forensic Sci Int Genet* 2011;5(1):27–32.
7. Ferragut JF, Bentayebi K, Castro JA, et al. Genetic analysis of 12 X-chromosome STRs in Western Mediterranean populations. *Int J Legal Med* 2015;129(2):253–55.
8. Ferragut JF, Bentayebi K, Barbaro A, et al. Exploring the Western Mediterranean through the X-chromosome. *Int J Legal Med* 2021;135(3):787-90.
9. Tomas C, Sanchez JJ, Barbaro A, et al. X-chromosome SNP analyses in 11 human Mediterranean populations show a high overall genetic homogeneity except in North-west Africans (Moroccans). *BMC Evol Biol* 2008;29(8):75.
10. Robino C, Lacerenza D, Aneli S, et al. Allele and haplotype diversity of 12 X-STRs in Sardinia. *Forensic Sci Int Genet* 2018;33:e1–e3.
11. Tomas C, Skitsa I, Steinmeier E, et al. Results for five sets of forensic genetic markers studied in a Greek population sample. *Forensic Sci Int Genet* 2015;16:132–37.
12. Tillmar AO, Kling D, Butler JM, et al. DNA Commission of the International Society for Forensic Genetics (ISFG): Guidelines on the use of X-STRs in kinship analysis. *Forensic Sci Int Genet* 2017;29:269–75.

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Centenarians:

What Can They Teach Us About Lifespan & Healthspan?

ABSTRACT

The human lifespan has increased, and worldwide, the number of centenarians has increased exponentially. In their exceptional longevity, centenarians have a lower incidence of age-related diseases. Researching the underlying protective molecular mechanisms could potentially lead to discovering molecular targets which could be translated into therapeutic and possibly preventive interventions for healthy ageing.

INTRODUCTION

The human lifespan has increased, and worldwide, the number of centenarians has increased exponentially. Classically, 'blue zones' are five places in the world where centenarians and other old people live longest and healthiest. **The blue zones are Sardinia (Italy), Okinawa (Japan), Ikaria (Greece), Loma Linda (California) and Nicoya (Costa Rica).** Here, centenarians form a significant percentage of the population. And researchers have and are studying the local centenarians in order to underline the mechanisms of healthy ageing and longevity. Indeed, using the centenarians as a useful model for ageing, researchers are analyzing and focusing on the environmental and genetic dynamics to unlock the secrets of longevity.

Generally, common people have some form of disease 5 to 8 years before they die. But many centenarians are relatively healthy and keep their abilities up till some months before they die. This means that their debilitating diseases occur in a very compressed time frame. However, this does not imply that their body are young. Indeed, many experience some disability in their mobility, eyesight and hearing. But by and large, they do not suffer from major diseases like diabetes, cardiovascular disease, cognitive decline and cancer that may afflict normal persons that die in their seventies.

One might think that centenarians have these health benefits because they follow a healthy lifestyle. But in many instances, this is not always the case. In the 'The Longevity Genes Project', Dr Nir Barzilai and his team, at the Albert Einstein College of Medicine, US, found that a relatively high percentage were overweight, smoked and did not do moderate exercise. From Dr Barzilai's project, estimates for ageing show that for most people, nurture accounts for 80% and genetics accounts for the rest, whilst for centenarians, genetics accounts for 80% and the environment accounts for 20%. This gives scope to research and look for 'longevity genes'. It is proposed that the knowledge gained will then be used to offer protection from the ageing that centenarians enjoy.

Indeed, research is being directed to decipher how centenarians are living such long lives in such remarkable health. And researchers are using all the -omics (genomics, epigenomics, transcriptomics, proteomics, metabolomics) and more, to unlock the secrets of longevity, which will surely benefit humanity in general.

EPIGENETICS IN CENTENARIANS

Epigenetics is one of the very promising fields in the study of ageing and longevity. And this makes sense because epigenetics is the molecular landscape where genetics and the environment interact with each other. Moreover, this interaction then has ripple effects on the

cellular dynamics, whose alterations are studied through the various –omic fields and more, making the complex puzzle pieces fit together. Furthermore, studies have shown that the epigenetic landscape is dynamic and flexible and certain alterations in it that are conducive to disease are possibly reversible, offering scope for both prevention and treatment.

DNA methylation is a universal epigenetic mechanism controlling chromatin organization and thus its accessibility for transcription. DNA methylation is regularly associated with a compact chromatin status, rendering it less accessible to binding of transcription factors and chromatin remodelling complexes. Generally, epigenetic studies show that normally there is a loss of genome-wide DNA methylation associated with ageing and age-related diseases. However, epigenetic studies in centenarians show that they better preserve their DNA methylation status.[1,2] Furthermore, **centenarians pass this better preservation of their DNA methylation status to their offspring.**

This better preservation of their DNA methylation might imply that transposon sites in the DNA are better kept from being transcribed and thus prevented from causing havoc (see below, transposon theory of ageing).

Dr Steve Horvath, a professor at UCLA, pioneered the first "age clock" based on DNA methylation chemical changes to indicate human ageing. Today, many companies advertise such 'epigenetic clock' tests to distinguish between real age and biological age. Many believe that such information on epigenetic drift with ageing can provide insight into the ageing process that, if used correctly, can help us to make interventions to lengthen our lives. Others rightly debate and believe that ageing is much more complicated than just some DNA alterations. The FDA has not approved any of these tests. And yet researchers continue in their quest to come up with a biological test that will be reliable enough for doctors to base their health recommendations.

GENOMICS

As already said above, genetics plays a significant role in the longevity of centenarians. Thus, some research is focused on looking for 'longevity genes'. Having said this, probably as longevity is a polygenic trait, it depends on the collective small influence of many genes. Genetic studies, like GWAS (Genome Wide Association Studies) of families with long-lived individuals, indicate a longevity locus on chromosome 3, more specifically the 5q33.3 locus,[3] which has been found to be associated with a healthy cardiovascular system and healthy physical functioning.

Other studies point to gene variants of APOE (Apolipoprotein E) and FOXO3A (forkhead box O3A) genes.[4] APOE gene is located on chromosome 18, and FOXO3A is located on chromosome 6. The APOE gene codes for a major apoprotein in chylomicrons and functions in the normal catabolism of lipoproteins rich in triglycerides. FOXO3a is a transcription factor. One function of FOXO3a is to suppress mutations resulting from DNA double-strand breaking. It is proposed that it binds to genes which are then expressed to bring about apoptosis (programmed cell death).

Other genes implicated as candidates for longevity in centenarians are IGF1 (Insulin-Like Growth Factor 1), located on chromosome 12 and CETP (cholesteryl ester transfer protein), located on chromosome 16. IGF1 codes for Insulin-Like Growth Factor 1, which has protective effects against atherosclerosis. CETP codes for a protein which participates in the transfer of cholesteryl ester from HDL (high density lipoprotein) to other lipoproteins.[5]

TRANSCRIPTOMICS

Transcriptomics is the study of the transcriptome, the latter being the collection of RNAs transcribed and that includes tRNA (transfer RNA), rRNA (ribosomal RNA), mRNA (messenger RNA) and ncRNA (noncoding RNA). Its profiling is also providing more insight into longevity.

Karagiannis et al.[6] profiled the transcriptome of mononuclear cells in the peripheral blood of a centenarian cohort. Their study confirmed the established trends with ageing in the immune cell populations, specifically the swing of lymphocytes to myeloid cells, and noncytotoxic cells to cytotoxic cells. Moreover, they found a shift in the population of CD4+ T cells to B cells. Furthermore, they found higher expression of STK17A (Serine/Threonine Kinase 17a) and S100A4 (S100 calcium binding protein A4) genes. STK17A is located on chromosome 7 and codes for a protein that has apoptosis-inducing activity in response to DNA damage. S100A4 is located on chromosome 1 and codes for a protein that belongs to the S100 protein family. These S100 proteins regulate several processes inside cells, like differentiation, cell cycle progression, tubulin polymerization, motility, and invasion. Karagiannis et al. propose that their findings implicate a unique elite immunity in centenarians that remains functional in their exceptional longevity.

Jiang et al.[7] studied the differential expression of long noncoding RNAs (lncRNAs) in peripheral blood samples. They found eight lncRNAs that were differentially expressed and thus proposed them as healthy ageing candidates. Of these eight lncRNAs, two (THBS1-IT1 and THBS1-AS1) were relatively more expressed. THBS1-IT1 (Thrombospondin 1-Intronic Transcript 1) and THBS1-AS1(Thrombospondin 1-Antisense RNA 1) slow down cellular senescence, and so the researchers propose them as prospective molecules involved in the anti-ageing pathways.

In their study, Yang et al.[8] built on the established knowledge that TGF-β (Transforming Growth Factor-beta) superfamily has anti-ageing functions. Indeed, they looked for variants of TGF-β genes. They used a cohort of Ashkenazi Jewish centenarians and found a variant in the SMAD3 (mothers against decapentaplegic homolog 3) gene, which is located on chromosome 15. This gene codes for a protein that participates in the TGF-β pathway, a transduction pathway that passes environmental signals from the cell surface to the nucleus, affecting cellular functions like proliferation, movement and apoptosis (controlled cell death) of cells. From further studies on iPSCs (induced pluripotent stem cells) and a progeroid mouse model, they showed that the SMAD3 variant resulted in decreased senescence and inflammation in endothelial cells. And this, they propose, could be another factor in human longevity. They also suggest that SMAD3 could be a potential molecular target in the quest to develop drugs that could extend longevity.

Micro-RNA (miRNAs) related to longevity have also been studied. Indeed, Serna et al.[9] in their study compared the microRNA signatures in mononuclear cells of centenarians, octogenarians and young individuals. Centenarians showed a microRNA profile that overlapped that of the young individuals but not that of octogenarians. Moreover, 4 miRNAs were significantly overexpressed in centenarians. These miRNAs (Table 1) were miR-21, miR-130a, miR-494 and SCARNA17 (small Cajal body-specific RNA 17).

Table 1. miRNAs which are significantly overexpressed in centenarians.

Up-regulated miRNA	Possible Function
miR-21	Protection from ischemia of neurons[10] and heart[11,12]; Protection from mitochondrial damage[13]
miR-130a	Suppression of myocardial ischemia reperfusion[14]
miR-494	Protection against Ischemia/Reperfusion-Induced Cardiac Injury[15]
scaRNA17	Maintenance of RNA-related metabolic processes and telomere processes[16]

PROTEOMICS

Proteomics is the analytical study of all proteins transcribed by a genome. It varies temporally and spatially according to the distinct needs of the organism. Proteomics is another –omic tool in ageing research. Frankowska et al.[17] did a proteomic study based on their hypothesis that centenarians keep a cellular proteome that is 'young'. Their study confirmed that centenarians have protein dynamics very similar to those of young individuals.

Sebastiani et al.[18] also found similar 'young' signatures in centenarians. Moreover, they also found a list of serum proteins that could be used to estimate cellular senescence. They propose that these signatures could be possible biomarkers of longevity and healthy ageing, and also that they could imply prospective target molecular mechanisms for a long, healthy life.

Santos-Lozano et al.[19] found differential protein expressions in centenarians when compared to controls. Specifically, they found proteins and pathways linked to a healthy immune system (distinctively less inflammation, less autoimmunity and preserved B cell-mediated immune response). They also found that centenarians have a lower protein expression profile than individuals who have cardiovascular disease. Moreover, they found that the studied centenarians have a healthy protein expression involved in angiogenesis and intercellular junctions. They pinpoint the fact that various conditions are associated with cell junction disruptions. Examples include neuro-degeneration[20], cardiovascular disease[21] including cardiomyopathies[22], type 2 diabetes mellitus[23], and autoimmunity[24].

METABOLOMICS

Metabolomics is the process whereby metabolites are profiled in biofluids, cells and tissues. With the advances of informatics and other analytical technologies, metabolomic profile analyses are also being used to understand the physiological and pathophysiological mechanisms of ageing in centenarians.

Collino et al.[25] studied the metabolic profiles of a cohort of Italian centenarians to discover the biological mechanism of longevity. They found that the metabolic longevity phenotype shows an adaptation in the metabolism of lipids, amino acids and microbiota. They propose that this remodelling reflects the ability of centenarians to adapt or respond to the build-up of oxidative and inflammatory insults over their long life.

Cai et al.[26] found similar results (and more) in a cohort of thirty healthy Chinese centenarians. Specifically, they found 69 metabolites that were differentially expressed in the centenarians when compared to controls. From these metabolites, they identified 6 metabolic pathways which are implicated in benefiting cognition, anti-inflammatory processes (phagocytosis, immune response), glucose and lipid metabolism, suppression of oxidative damage, protein glycation, and scavenging of harmful molecules that tend to accumulate with long age. In their paper, they go in depth on specific metabolites and the beneficial pathway/s they are involved in.

TRANSPOSONS

A transposon is a piece of DNA sequence that can move from one position to another position in the genome. The human genome harbours such sequences. Transposons are held in check from doing deleterious effects (like gene mutations) in the genome by several mechanisms, one of which is epigenetic in nature (namely DNA methylation, histone modifications and small non-coding RNAs). Transposons are being implicated to have physiological and pathological functions in the genomes of the cells that host them. Indeed, accumulating evidence is showing that they may be associated with certain human diseases, like rheumatoid arthritis, insulin-dependent diabetes mellitus, neurological diseases (e.g. schizophrenia, multiple sclerosis, motor neuron disease) and cancer. Understanding how these transposons bring about these human diseases could help in their prevention and treatment.[27]

This knowledge begs the question, 'Could centenarians have better systems to keep in check these transposons, that if unleashed could cause havoc in the genome and hence bring on disease?' Research along the hypothesis that transposons might be responsible for ageing (transposon theory of ageing) is ongoing. Simon et al.[28] found a variant of Sirtuin 6 (SIRT6) in Ashkenazi Jewish centenarians. Sirtuin 6 (SIRT6) is implicated in ageing and in the regulation of metabolism. It does so via multiple pathways in the cell. They found that this variant of SIRT6 (centSIRT6) enhances human longevity by maintaining the human genome. Specifically, this variant confers better suppression of LINE1 (long interspersed nuclear elements 1) retrotransposons, better repair of breaks in the DNA double strand, and also offers better protection against cancer cells.

Another mechanism is the preferential insertions of LINE1 (L1) sequences to gene-poor regions like those found in chromosome 13.[29,30] Chromosome 13 (like chromosome 18, 21, and Y) is a gene-poor chromosome. Thus, new insertions of L1s will unlikely disrupt any important gene loci.

STEM CELLS

The functions of stem cells (like repairing or regenerating tissues) deteriorate as humans age.[31] It is believed that this deterioration in stem cell functions plays an important role in the ageing process and its associated disorders. Indeed, in the 'stem cell theory of ageing', it is hypothesized that ageing is due to the failure of stem cells to renew themselves and provide repair.[32,33]

Ingles et al.[34] using peripheral blood mononuclear cells (PBMCs) in centenarians found that they up-regulate the transcription factors called Yamanaka Factors (i.e. OCT3/4, SOX2, and c-MYC) and other genes (VIM, NCAM, BMP4, and BMPR2) that implicate stemness. They also found up-regulation of BCL-xL (B-Cell Lymphoma-extra-large), a mitochondrial protein which promotes cell survival by inhibiting apoptosis. BCL-xL is also involved in senescence and autophagy pathways. The authors propose that their findings might be one mechanism that explains why centenarians have a unique and efficient cell homeostasis, enabling them to live a long and healthy life.

TELOMERES

Telomeres are structures that protect chromosomal ends. Some telomere research is also the focus of ageing research. Specifically, as a chromosome replicates, its telomere shortens, and its length makes it an approximate gauge of biological ageing and mortality.

Tedone et al.[35] compared the frequency of age-related diseases and telomere length in centenarians and their offspring. They discovered that centenarians and their offspring preserve better telomere length. They propose that this superior maintenance might play a part in their longevity and health.

TRANSLATIONAL RESEARCH

The research on centenarians is showing the underlying main hallmarks of ageing, namely inflammation, loss of proteostasis, stem cell exhaustion, metabolic dysregulation, epigenetic aberrations, failure of chromosome maintenance (DNA repair, telomere erosion), cellular senescence, mitochondrial dysfunction, altered intercellular communication and immunity failure. It also shows that there is connectivity between these hallmarks, and it is proposed that one can target one hallmark and also get improvements in the others. The holy grail of gero-therapeutics is targeting such pathway/s to increase human healthspan and lifespan.

One way forward will surely be non-coding RNA-based therapy. Some of the physiological and pathophysiological roles of non-coding RNAs (ncRNAs) associated with ageing have already been discovered. These discoveries have been pivotal in providing insight into the basis of various ageing diseases where ncRNAs are aberrantly expressed. Already, translational

research uses these ncRNAs mechanisms for theranostics. Presently, the main players in non-coding RNA-based therapies include antisense oligonucleotides, locked nucleic acid anti-miRs, miRNA sponges, miRNA mimics, siRNAs and ribozymes. Grech et al.[36] discuss this in their paper.

One gero-therapeutic that is being evaluated for its protective effect against ageing is Metformin.[37] Indeed, studies are showing that it impacts many of the mentioned main hallmarks of ageing and thus has the potential to modulate ageing and treat diseases associated with ageing.

CONCLUSION

Many of the chronic human diseases have ageing as the underlying risk factor. Using centenarians as an ageing model has led to the concerted discovery of conserved molecular pathways associated with extended lifespan and healthspan. Hopefully, these insights will offer molecular druggable targets to develop gerotherapeutic interventions to extend and maximize human healthspan ... some even believe in the possibility of ageing reversal.[38] Moreover, these insights will lead to the discovery of biomarkers that are predictive of healthy ageing, making the latter's medical and socio-economic benefits feasible.

REFERENCES

1. Gentilini D, Mari D, Castaldi D, et al. Role of epigenetics in human aging and longevity: genome-wide DNA methylation profile in centenarians and centenarians' offspring. *AGE* 2013;35:1961–1973.
2. Daunay A, Hardy LM, Bouyacoub Y, et al. Centenarians consistently present a younger epigenetic age than their chronological age with four epigenetic clocks based on a small number of CpG sites. *Aging* 2022;14:7718–7733.
3. Nygaard M, Thinggaard M, Christensen K, et al. Investigation of the 5q33.3 longevity locus and age-related phenotypes. *Aging* 2017;9:247–255.
4. Brooks-Wilson, AR. Genetics of healthy aging and longevity. *Human Genetics* 2013;132:1323–1338.
5. Capri M, Santoro A, Garagnani P, et al. Genes of Human Longevity: An Endless Quest?*Current Vascular Pharmacology* 2014;12(5):707–717.
6. Karagiannis TT, Dowrey TW, Villacorta-Martin C, et al. Multi-modal profiling of peripheral blood cells across the human lifespan reveals distinct immune cell signatures of aging and longevity. *eBioMedicine* 2023;90:104514.
7. Jiang J, Cheng L, Yan L, et al. Decoding the role of long noncoding RNAs in the healthy aging of centenarians. *Briefings in Bioinformatics* 2021;22(5):bbaa439.
8. Yang J, Tare A, Zhang L, et al. Longevity-associated SMAD3 non-coding centenarian variant impairs a cell-type specific enhancer to reduce inflammation. *bioRxiv* 2023:05.17.540984.
9. Serna E, Gambini J, Borras C, et al. Centenarians, but not octogenarians, up-regulate the expression of microRNAs. *Scientific Reports* 2012;2:961.
10. Buller B, Liu X, Wang X, et al. MicroRNA-21 protects neurons from ischemic death. *FEBS* 2010;277(20):4299–4307.
11. Dong S, Cheng Y, Yang J, et al. MicroRNA Expression Signature and the Role of MicroRNA-21 in the Early Phase of Acute Myocardial Infarction. *Journal of Biological Chemistry* 2009;284(43):29514–29525.
12. Cheng Y, Zhu P, Yang J, et al. Ischaemic preconditioning-regulated miR-21 protects heart against ischaemia/reperfusion injury via anti-apoptosis through its target PDCD4. *Cardiovascular Research* 2010;87(3):431–439.
13. Sayed D, He M, Hong C, et al. MicroRNA-21 Is a Downstream Effector of AKT That Mediates Its Antiapoptotic Effects via Suppression of Fas Ligand. *Journal of Biological Chemistry* 2010;285(26):20281–20290.
14. Li Y, Zhang H, Li Z, et al. microRNA-130a-5p suppresses myocardial ischemia reperfusion injury by downregulating the HMGB2/NF-κB axis. *BMC Cardiovascular Disorders* 2021;21:121.
15. Wang X, Zhang X, Ren X-P, et al. MicroRNA-494 Targeting Both Proapoptotic and Antiapoptotic Proteins Protects Against Ischemia/Reperfusion-Induced Cardiac Injury. *Circulation* 2010;122(13):1308–1318.
16. Zhao Y, Abreu E, Kim J, et al. Processive and Distributive Extension of Human Telomeres by Telomerase under Homeostatic and Nonequilibrium Conditions. *Molecular Cell* 2011;42(3):297–307.
17. Frankowska N, Bryl E, Fulop T, et al. Longevity, Centenarians and Modified Cellular Proteodynamics. *International Journal of Molecular Sciences* 2023;24(3):2888.
18. Sebastiani P, Federico A, Morris M, et al. Protein signatures of centenarians and their offspring suggest centenarians age slower than other humans. *Aging Cell* 2021;20(2):e13290.
19. Santos-Lozano A, Valenzuela PL, Llavero F, et al. Successful aging: insights from proteome analyses of healthy centenarians. *Aging* 2020;12(4):3502–3515.
20. Erdık F, Denes L, de Lange E. Age-associated physiological and pathological changes at the blood–brain barrier: A review. *Journal of Cerebral Blood Flow & Metabolism* 2017;37(1):4–24.
21. Li C, Gao M, Zhang W, et al. Zonulin Regulates Intestinal Permeability and Facilitates Enteric Bacteria Permeation in Coronary Artery Disease. *Scientific Reports* 2016;6:29142.
22. Mezzano V, Sheikh F. Cell–cell junction remodeling in the heart: Possible role in cardiac conduction system function and arrhythmias? *Life Sciences* 2012;90(9–10):313–321.
23. Jayashree B, Bibin YS, Prabhu D, et al. Increased circulatory levels of lipopolysaccharide (LPS) and zonulin signify novel biomarkers of proinflammation in patients with type 2 diabetes. *Molecular and Cellular Biochemistry* 2014;388:203–210.
24. Fasano A. Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer. *Physiological Reviews* 2011;91(1):151–175.
25. Collino S, Montoliu I, Martin F-PJ, et al. Metabolic Signatures of Extreme Longevity in Northern Italian Centenarians Reveal a Complex Remodeling of Lipids, Amino Acids, and Gut Microbiota Metabolism. *PLOS ONE* 2013;8(3):e56564.
26. Cai D, Zhao Z, Zhao L, et al. The Age-Accompanied and Diet-Associated Remodeling of the Phospholipid, Amino Acid, and SCFA Metabolism of Healthy Centenarians from a Chinese Longevous Region: A Window into Exceptional Longevity. *Nutrients* 2022;14(20):4420.
27. Grech A, Baldacchino S, HERVs, Transposons and Human Diseases: Part III. *The Synapse* 2013;12(2):9-11.
28. Simon M, Yang J, Gigas J, et al. A rare human centenarian variant of SIRT6 enhances genome stability and interaction with Lamin A. *The EMBO Journal* 2022;41(21):e110393.
29. Bojang Jr P, Anderton MJ, Roberts RA, et al. De novo *LINE-1*retrotransposition in HepG2 cells preferentially targets gene poor regions of chromosome 13. *Genomics* 2014;104(2)96–104.
30. Esnault C, Millet J, Schwartz O, et al. Dual inhibitory effects of APOBEC family proteins on retrotransposition of mammalian endogenous retroviruses. *Nucleic Acids Research* 2006;34(5):1522–1531.
31. López-Otín C, Blasco MA, Partridge L, et al. The Hallmarks of Aging. *Cell* 2013;153(6):1194–1217.
32. Smith JA,& Daniel R. Stem Cells and Aging: A Chicken-Or-The-Egg Issue?*Aging and Disease* 2012;3(3):260–268.
33. Shin J, Mohrin M, & Chen D. Reversing stem cell aging. *Oncotarget* 2015;6:14723–14724.
34. Inglés M, Mas-Barques C, Berna-Erro A, et al. Centenarians Overexpress Pluripotency-Related Genes. *The Journals of Gerontology: Series A* 2019;74(9):1391–1395.
35. Tedone E, Arosio B, Gussago C, et al. Leukocyte telomere length and prevalence of age-related diseases in semisupercentenarians, centenarians and centenarians' offspring. *Experimental Gerontology* 2014;58:90–95.
36. Grech A, West S. Non-Coding RNA-Based Therapy. *The Synapse* 2022;21(3)18–20.
37. Kulkarni AS, Gubbi S, Barzilai N. Benefits of Metformin in Attenuating the Hallmarks of Aging. *Cell Metabolism* 2020;32(1):15–30.
38. Yang J-H, Petty CA, Dixon-McDougall T, et al. Chemically induced reprogramming to reverse cellular aging. *Aging* 2023;15(13):5966–5989.

DR ANDREI AGIUS ANASTASI, MS FRANCESCA VELLA

Bridging Perspectives -

Rehabilitation Expectations Among Healthcare Professionals and the General Public

ABSTRACT

This study explores the perspectives of healthcare professionals and the public on current rehabilitation services and expectations for future improvements in Malta. Conducted as part of the "Just 3 Things" campaign, participants responded to three open-ended questions related to rehabilitation via an online questionnaire. A mixed-methods analysis revealed shared expectations for holistic, patient-centred care, as well as distinct priorities between the two groups. Findings highlight the need for modern infrastructure, improved access, emotional support, and the integration of more advanced technologies. These insights can inform policies and optimise service design that better aligns with the needs of all stakeholders.

INTRODUCTION

Rehabilitation is an essential pillar of healthcare, focused on enabling individuals to regain or improve function and reintegrate into daily life following injury, illness, or disability. This has more recently been highlighted by the 2023 World Health Assembly's resolution "Strengthening Rehabilitation in Health Systems," which calls for stronger integration of rehabilitation services within health systems and increased investment worldwide.[1]

In Malta, rehabilitation services have developed over the past two decades. Initially centred at Zammit Clapp Hospital under geriatric leadership, along with spinal rehabilitation at Boffa Hospital, services moved to Karin Grech Rehabilitation Hospital (KGRH) in 2007, where the first dedicated Physical and Rehabilitation Medicine (PRM) ward was established, led by a physiatrist, working alongside geriatric specialists across seven other wards. Over the years, the service has expanded to include two PRM wards - each with 30 beds - supported by two new PRM consultants and two higher specialist trainees in PRM, catering to patients of all ages with a range of conditions such as stroke, spinal cord injuries, amputations, and orthopaedic trauma.

Over the past few years, the Maltese Society of Physical and Rehabilitation Medicine (MSPRM) has played an active role in advocating for increased awareness and the need for development of rehabilitation services in Malta. The "Just 3 Things" campaign[2] is one such initiative, designed to collect grassroots feedback from both professionals and the general public. This study forms part of that initiative and aims to identify shared and divergent expectations for rehabilitation services in Malta.

METHODOLOGY

An online questionnaire was distributed to healthcare professionals and members of the general public after seeking approval from the ethics and data protection officers of Karin Grech Rehabilitation Hospital. This was done by emailing all Karin Grech Rehabilitation Hospital employees, through posts on social media of the Maltese Society of Physical and Rehabilitation Medicine (MSPRM), emails to other association

members such as the Geriatric Medicine Society Malta, and finally by distributing a physical questionnaire or QR code to all inpatients admitted at the time in the two PRM wards. The questionnaire included demographic questions covering age, occupation, and experience with rehabilitation (if any), along with three open-ended questions regarding expectations for current services, future improvements, and desired changes:

1. **What do you expect from rehabilitation services?**
2. **What ideas do you have for improving the current national rehabilitation services?**
3. **What would you want out of our future rehabilitation services?**

A link to the online questionnaire was also sent to all KGRH employees through their official email. The online questionnaire was also shared on the MSPRM webpage and social media, and other communication groups such as the PRM WhatsApp group. Flyers with the link and QR code were also printed and shared with patients and relatives on the two PRM wards at KGRH, along with those attending outpatients services in Saint Luke's Hospital.

Data from the online questionnaire were subsequently downloaded and analysed, extracting common themes and stratifying these according to whether responders were healthcare professionals or not.

RESULTS

A total of 50 responses were received:

- 34 (68%) from healthcare professionals, including nurses (31%), occupational therapists (16%), physiotherapists (13%), doctors (9%), pharmacists (3%) and others (13%).
- 16 (32%) from non-healthcare respondents.

The key themes extracted through a comparative analysis of all questionnaires can be categorised into eight main groups, as shown in Table 1.

HEALTHCARE PROFESSIONALS AND GENERAL PUBLIC RESPONDERS SHOWED A BROAD CONSENSUS REGARDING THE NEED FOR INVESTMENT IN REHABILITATION

Most of the themes had common alignment, with similar responses, between healthcare workers and general public respondents. For example, the idea that "Rehabilitation should be team-led, where all professions contribute equally", expressed by healthcare workers, was similar to the general public response of "[expecting] to be taken care of by a full team who knows my needs." Other themes had a somewhat different perspective on a similar topic, such as the wish "to invest in tech like Viral Reality and better IT systems" expressed by healthcare workers when compared to the general public's wish for "More equipment [which] would make therapy less boring and more helpful."

Other themes showed divergence in focus, such as those questions relating to infrastructure, where healthcare professionals expressed that "Each ward should have a gym [and] more equipment", while general public responses focused more on their concern that "The hospital looks like it's stuck in the 1980s … it doesn't give hope." This was echoed by the patients' need "to feel supported after everything I've been through" when compared to the less emphatic priority of "psychological care [to] be integrated to improve outcomes" expressed by healthcare workers.

Healthcare professionals and general public responders showed a broad consensus regarding the need for investment in rehabilitation, although healthcare professionals focused on the need for "more conferences, in-house lectures, and case-sharing." On the other hand, the general public felt that "we need more awareness and better links with employment and education."

Table 1. Summary of Key Themes: Comparison Between Healthcare Professionals and General Public.

	Theme	Healthcare Professionals	General Public	Comparative Analysis
1	Holistic, Multidisciplinary Care	Stressed the importance of equal contribution from all MDT and the inclusion of underrepresented professionals such as social workers and psychologists.	Focused on visible collaboration and the overall sense of being cared for by a cohesive team.	**Convergent opinion** - Both groups emphasized the need for a team-based, interdisciplinary approach to rehabilitation that addresses not only physical but also emotional, social, and functional dimensions.
2	Patient-Centred & Individualised Care	Highlighted structured goal-setting, empowerment, and case conferencing.	Described the desire for empathy, attention, and the feeling of being "seen."	**Convergent opinion** - Strong alignment in advocating for personalized rehabilitation plans that respect the patient's goals, autonomy, and dignity.
3	Accessibility & Continuity	Discussed systemic challenges, such as staffing limitations and poor interdepartmental coordination.	Focused more on practical accessibility (e.g. transportation, easy appointment scheduling).	**Convergent opinion** - Both groups cited issues with fragmented services and long wait times, along with the need for community outreach and telerehabilitation
4	Facilities & Environment	Critiqued outdated equipment and lack of space, especially in gym areas.	Described the current facilities as demoralizing and compared them unfavourably to hospitals abroad.	**Divergent focus** - Both groups acknowledged the inadequacy of current infrastructure, but the public was more emotionally affected by the environment.
5	Workforce & Training	Emphasized the need for more staff, longer service hours, and continuous training, including international exposure.	Less focus placed on staff development, though respondents expressed appreciation for professionalism and competence.	**Divergent focus** - predominantly a healthcare worker concern
6	Emotional & Psychological Support	Mentioned the need for psychological services, but less frequently than the general public responders	Expressed the need for emotional reassurance and trauma recovery.	**Divergent focus** - Emotional security and mental health support were more commonly emphasized by the general public, especially among those with direct experience (patients rather than relatives).
7	Innovation & Technology	Advocated for tools like VR and digital record-keeping to enhance therapy and coordination.	Emphasized how modern tools can make therapy more interesting and effective.	**Convergent ideas** - Both groups supported the introduction of advanced technologies, though professionals focused on clinical efficiency, while the public valued patient engagement.
8	Future Vision	Called for more research, training, and interprofessional learning	Advocated for public awareness, better integration with education/ employment services	**Convergent ideas** - Both groups highlighted the importance of expanding services, educating the public, and advocating for the role of rehabilitation.

DISCUSSION

This study reveals significant convergence between healthcare professionals and the public in advocating for holistic, patient-centred care and increased investment in rehabilitation services. Stakeholders from various settings strongly align with the WHO Rehabilitation 2030 initiative,[1] supporting integrated, well-funded rehabilitation services and emphasizing workforce development and governance.[3,4,5]

However, notable divergences also emerged. Healthcare professionals prioritized systemic improvements, such as staffing, infrastructure, and service delivery models, reflecting broader challenges in healthcare systems, such as resource limitations and workforce gaps.[6] In contrast, the public focused more on emotional support, care coordination, and the physical environment of healthcare settings. This study highlights that patients value relational aspects of care, such as communication and emotional reassurance, nearly as much as clinical outcomes.[7,8]

The integration of emotional support and mental health services is vital to bridging the gap between the priorities of healthcare professionals and the public. While healthcare professionals acknowledged the importance of psychological support, it was not as central to their priorities, underscoring the need for a greater focus on mental health services and emotional well-being in rehabilitation care.[9]

Accessibility emerged as a shared concern, though perceived differently. Professionals often focused on systemic issues like capacity and workforce, while patients identified immediate logistical barriers and scheduling challenges.[10,11] These discrepancies align with other studies, suggesting that system planners often overlook the practical challenges faced by patients.[12,13] Strengthening outpatient services and incorporating solutions like telerehabilitation could help address these barriers.[14]

Both patients and healthcare professionals expressed optimism about the role of technology in enhancing engagement and improving efficiency. This aligns with growing evidence supporting the use of digital tools and telerehabilitation in rehabilitation.[15,16] Additionally, both groups showed interest in

MALTA IS WELL-POSITIONED TO ADVANCE REHABILITATION AS A CENTRAL AND DYNAMIC COMPONENT OF ITS HEALTHCARE SYSTEM

long-term strategies, including public education, cross-sector collaboration, and sustained investment, which could help address barriers and facilitate the integration of technology in rehabilitation care.[17]

This study had a number of limitations worth noting. First, the sample size was relatively small (n = 50), which limits the statistical power and generalizability of the findings. However, the study did successfully include key stakeholders in the current rehabilitation system, as well as a number of patients actively undergoing rehabilitation. Second, the inclusion of detailed demographic information - while helpful for context - may have compromised respondent anonymity. This could have influenced the candor of some responses, particularly among identifiable participants. Despite these limitations, the study conveys an important message: Malta's plans for a new dedicated rehabilitation hospital represent a valuable opportunity to better align services with both clinical goals and patient-centred priorities. Actively involving healthcare professionals and the public in the planning and design process could help establish Malta as a leader in inclusive and progressive rehabilitation care models.

CONCLUSION

There is substantial alignment between healthcare professionals and the public in envisioning the future of rehabilitation in Malta: person-centred, emotionally supportive, and accessible care delivered in modern, well-resourced settings. Bridging the gap between system-level and experiential priorities will be key to future progress. Grounded in both local insight and international frameworks such as the WHO *Rehabilitation 2030* agenda, Malta is well-positioned to advance rehabilitation as a central and dynamic component of its healthcare system.

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REFERENCES

1. World Health Organization. Resolution: *Strengthening rehabilitation in health systems*; 2023 [Internet]. Available from: https://apps.who.int/gb/ebwha/pdf_files/EB152/B152(10)-en.pdf
2. Maltese Society of Physical and Rehabilitation Medicine. *Just 3 Things Campaign*. [Online] Available at: https://msprm.org.mt/#just-3-things Maart R, Mji G, Morris LD, et al. The rehabilitation landscape in a low-to-middle-income country: stakeholder perspectives and policy implications—a qualitative study. *Inquiry* 2024;61:469580241230916.
3. Neill R, Shawar Y, Ashraf L, et al. Prioritizing rehabilitation in low- and middle-income country national health systems: a qualitative thematic synthesis and development of a policy framework. *Int J Equity Health* 2023;22(1):122.
4. Watkins K, Levack W, Rathore FA, et al. What would 'upscaling' involve? A qualitative study of international variation in stroke rehabilitation. *BMC Health Serv Res* 2021;21(1):312.
5. Goldman AJ, Jones ON, Malina BL, et al. Rural needs and gaps in stroke rehabilitation: results of statewide healthcare provider and patient survey. *Arch Phys Med Rehabil* 2022;103(8):1551–1560
6. Desveaux L, Goldstein R, Mathur S, et al. Barriers to physical activity following rehabilitation: perspectives of older adults with chronic disease. *J Aging Phys Act* 2016;24(2):223–233.
7. Hughes A, Burridge J, Demain S, et al. Translation of evidence-based assistive technologies into stroke rehabilitation: users' perceptions of the barriers and opportunities. *BMC Health Serv Res* 2014;14:124.
8. Nation L, Spence N, Parker S, et al. Implementing introductory training in trauma-informed care into mental health rehabilitation services: a mixed methods evaluation. *Front Psychiatry* 2022;13:951160.
9. Hasan M, Anusaksathien K, Narattharaksa K, et al. Factors relating to the expectations and perceptions of post-stroke outpatients in the rehabilitation services of Bangladesh. *Int J Stat Med Res* 2022;11(2):134–142.
10. Medina-Mirapeix F, Oliveira-Sousa S, Sobral-Ferreira M, et al. Continuity of rehabilitation services in post-acute care from the ambulatory outpatients' perspective: a qualitative study. *J Rehabil Med* 2011;43(1):58–64.
11. Cooke M, Thackray S. Differences between community professional and patient perceptions of chronic obstructive pulmonary disease treatment outcomes: a qualitative study. *J Clin Nurs* 2012;21(1–2):132–140.
12. Westby M, Backman C. Patient and health professional views on rehabilitation practices and outcomes following total hip and knee arthroplasty for osteoarthritis: a focus group study. *BMC Health Serv Res* 2010;10:119.
13. Tousignant M, Boissy P, Moffet H, et al. Patients' satisfaction of healthcare services and perception with in-home telerehabilitation and physiotherapists' satisfaction toward technology for post-knee arthroplasty: an embedded study in a randomized trial. *Telemed J E Health* 2011;17(5):376–382.
14. Brouns B, Meesters J, Wentink M, et al. Why the uptake of eRehabilitation programs in stroke care is so difficult—a focus group study in the Netherlands. *Implement Sci* 2018;13(1):133.
15. Miller AE, Holleran CL, Bland MD, et al. Perspectives of Key Stakeholders on Integrating Wearable Sensor Technology into Rehabilitation Care: A Mixed-Methods Analysis. medRxiv [Preprint]. 2024 Nov 29:2024.11.25.24317911.
16. Zanatta F, Giardini A, Pierobon A, et al. systematic review on the usability of robotic and virtual reality devices in neuromotor rehabilitation: patients' and healthcare professionals' perspective. *BMC Health Serv Res* 2022;22(1):478.

DR NATHAN EDWARDS

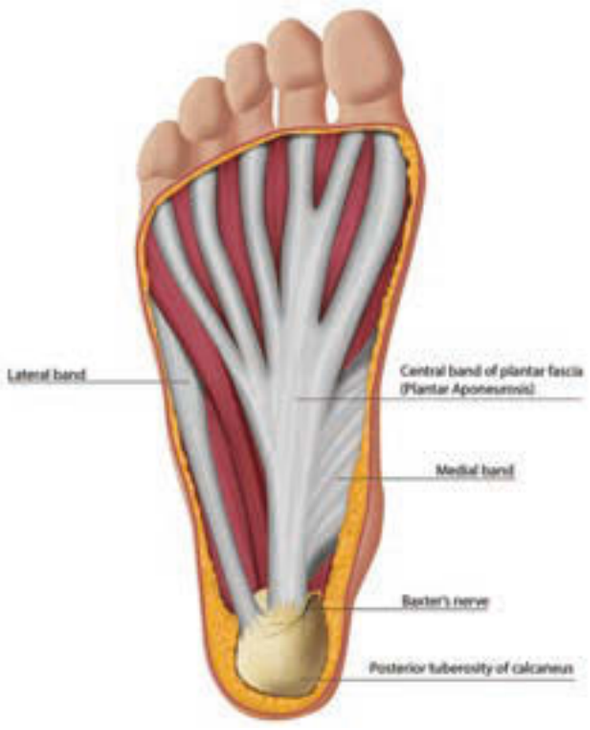
Plantar Fasciitis:

Radiological Findings and Evidence-Based Treatment Approaches

INTRODUCTION

The plantar fascia is a fibrous aponeurosis superficial to the intrinsic muscles of the foot, originating from the medial calcaneal tuberosity, and is integral to supporting the longitudinal arch. Anterior to the calcaneus, it extends forward and separates into medial, central, and lateral portions, and at the mid-sole level, it then splits into five bands which ultimately insert onto the bases of all five proximal phalanges as the plantar plates, respectively (Figure 1).[1,2]

Figure 1. Anatomy of the plantar fascia. Source: Latt D, Jaffe DE, Tang Y, et al. 2020.[3]



Plantar fasciitis, more accurately termed insertional plantar fasciopathy, is the most common cause of chronic plantar heel pain in adults, with a lifetime prevalence of 7-10%. It is primarily an overuse injury with repetitive strain causing microtears of the plantar fascia. Predisposing factors include prolonged standing or jumping, obesity, gastrocnemius-soleus tightness, pes planus and pes cavus, and limited ankle dorsiflexion. Most cases are self-limiting and resolve within 6-12 months, yet symptoms can be prolonged and functionally limiting.[4]

Despite this name suggesting inflammation, histological studies reveal that the condition is primarily characterized by degenerative changes rather than active inflammation, with findings including myxoid degeneration, collagen fragmentation, and vascular ectasia at the fascial attachment site to the calcaneus (angiofibroblastic hyperplasia). This distinction is clinically significant as this shifts the therapeutic approach from purely antigravity and anti-inflammatory strategies to those promoting tissue healing and remodelling.[5,6]

Plantar fasciitis is predominantly a clinical diagnosis, with imaging reserved for specific circumstances. Patients typically present with medial calcaneal tubercle tenderness, particularly during the first steps in the morning or after periods of rest, which improves with continued ambulation. A thorough history should explore recent increases in weight-bearing activities, changes in footwear, or occupational demands that might contribute to the condition. Key findings during clinical examination include tenderness to palpation of the proximal plantar fascial insertion on the anteromedial calcaneus, rather than directly under the heel.[5]

RADIOLOGICAL FINDINGS

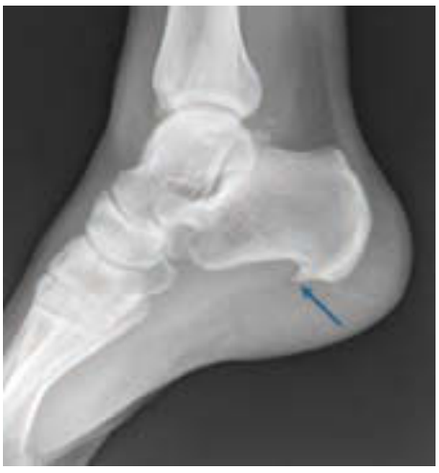
WHEN TO CONSIDER IMAGING

- Atypical clinical presentation (e.g. pain not localized to the medial calcaneal tuberosity).
- Pain persists despite 6-12 weeks of appropriate conservative management.
- Systemic symptoms suggest inflammatory arthropathy (classically a seronegative arthropathy, with bilateral involvement).
- Suspicion of an alternative diagnosis (e.g. calcaneal stress fracture, fat pad atrophy or referred pain from the lumbar spine).[7]

X-RAY FINDINGS

Conventional radiography remains an accessible first-line imaging modality when indicated. X-rays may reveal plantar calcaneal spurs (Figure 2). However, it is important to understand that plantar calcaneal spurs have also been observed in up to 25% of asymptomatic patients, so these may not be clinically predictive. Plain radiographs are primarily valuable for excluding other conditions such as calcaneal fractures, osteomyelitis or significant degenerative joint disease.[7,8]

Figure 2. Lateral ankle radiograph demonstrating a plantar calcaneal spur (arrow).



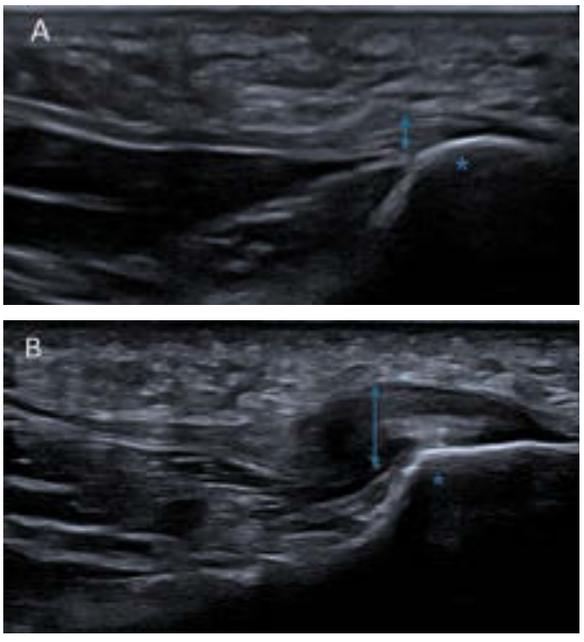
ULTRASOUND FINDINGS

Musculoskeletal ultrasound is a valuable tool for evaluating plantar fasciitis, offering real-time, dynamic assessment without radiation exposure. Key ultrasound findings include:

- Plantar fascia thickness greater than 4mm at the calcaneal insertion.
- Hypoechogenicity of the fascia, indicating structural disorganization.
- Perifascial fluid/oedema (less consistently present).
- Neovascularization on Doppler imaging (less consistently present).[9]

Figure 3 demonstrates the normal plantar fascia and the common sonographic findings noted in plantar fasciitis.

Figure 3. Longitudinal sonographic views of the plantar aspect of the foot demonstrating (A) the normal thickness (<4mm) shown by the two-headed arrow and echogenicity of the plantar fascia and (B) an abnormally thickened (>4mm) hypoechogenic plantar fascia. The Calcaneal tuberosity is marked by *.



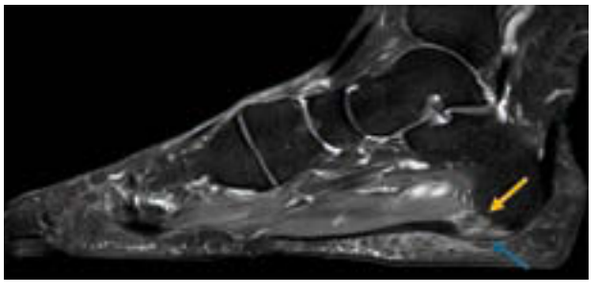
MRI FINDINGS

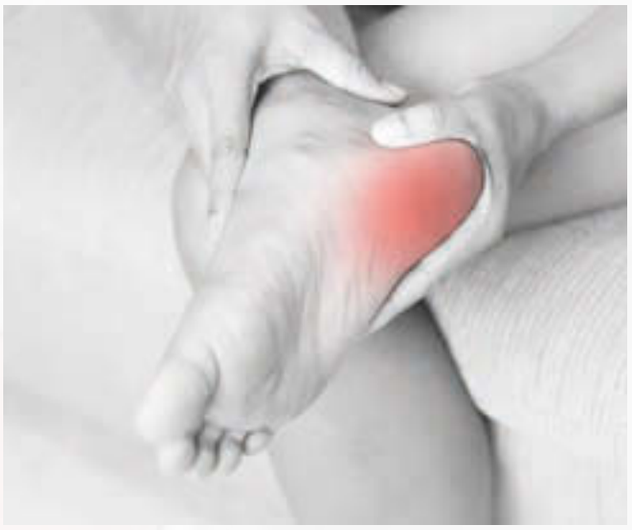
Magnetic resonance imaging offers the most comprehensive evaluation of plantar fasciitis and surrounding structures, though it is typically reserved for complex or refractory cases due to cost and availability considerations. Characteristic MRI findings in plantar fasciitis include (Figure 4):

- Plantar fascia thickness greater than 4mm at the calcaneal insertion.
- Increased signal intensity on fluid-sensitive sequences at the calcaneal insertion, indicating oedema and degeneration.
- Perifascial soft tissue oedema.
- Bone marrow oedema in the calcaneus in severe or chronic cases.

MR imaging is particularly valuable for differentiating plantar fasciitis from other causes of heel pain, such as plantar fascial tears, Baxter neuropathy, plantar fibroma, calcaneal stress fractures or tarsal tunnel syndrome.[9,10]

Figure 4. Sagittal fluid-sensitive fat-saturated sequence demonstrating a thickened oedematous plantar fascia at the calcaneal origin (blue arrow), together with calcaneal bone marrow oedema and a small plantar calcaneal spur (yellow arrow).





TREATMENT

A structured conservative approach should be adopted for at least 6-12 weeks. If pain remains moderate to severe and functionally limiting after optimizing conservative treatment, escalation to procedures supported by imaging should be considered, which occurs in approximately 5-10% of cases.

CONSERVATIVE TREATMENT APPROACHES

Plantar fascia-specific stretching represents the most evidence-based initial intervention. The most effective technique involves seated towel stretches, where the patient pulls the toes towards the shin with the knee extended, targeting the plantar fascia directly. Foot orthoses with emphasis on proper arch support and cushioning, and night splints maintaining the ankle in dorsiflexion have also been shown to provide moderate short-term pain relief.[11] Non-steroidal anti-inflammatory drugs may provide short-term symptomatic relief but have limited evidence for long-term benefit, and their use should be time-limited and balanced against potential gastrointestinal and cardiovascular risks, particularly in older patients.[4]

ADVANCED TREATMENTS - IMAGE-GUIDED AND DEVICE-BASED INTERVENTIONS

CORTICOSTEROID INJECTIONS

Corticosteroid injections can provide significant short-term pain relief (4-12 weeks), however should be limited to 1-2 per site, ideally with ultrasound guidance to ensure accurate needle placement and to minimize complications such as plantar fat pad dystrophy and plantar fascia rupture. A small volume of steroid is deposited around, not within, the fascia origin (Figure 5).[4] This may be combined with same-visit dry needling.

PLATELET-RICH PLASMA INJECTIONS

Ultrasound-guided platelet-rich plasma (PRP) injection represents a promising regenerative approach, delivering concentrated growth factors to stimulate tissue healing. This may provide superior long-term outcomes compared to corticosteroid injections, with a more favourable risk-benefit profile, particularly for patients with chronic symptoms. Percutaneous needle tenotomy or dry needling to produce microtears in the affected fascia to stimulate healing is often combined with PRP (Figure 6).[12]

Figure 5. (A) Short-axis in-plane technique for steroid infiltration of the plantar fascia with corresponding ultrasound image (B) demonstrating the needle path for superficial (blue arrow) and deep placement (yellow arrow) of the steroid.

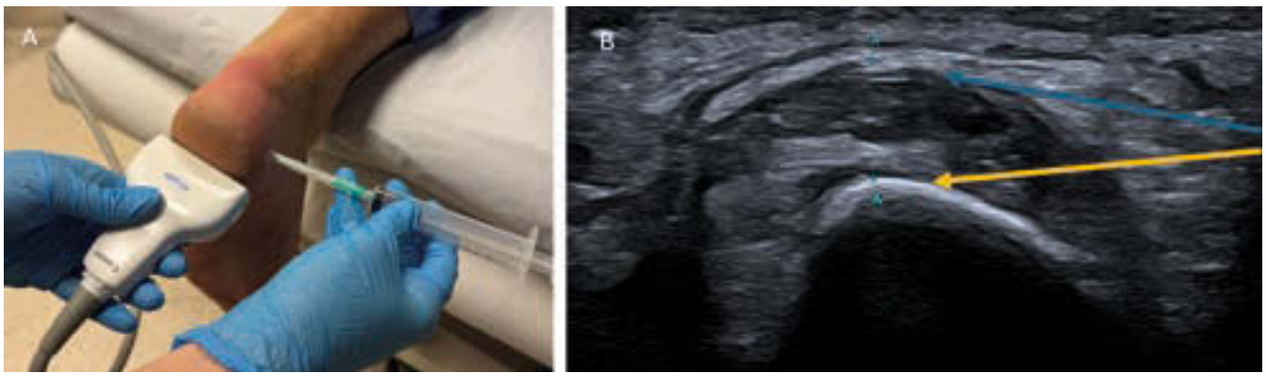
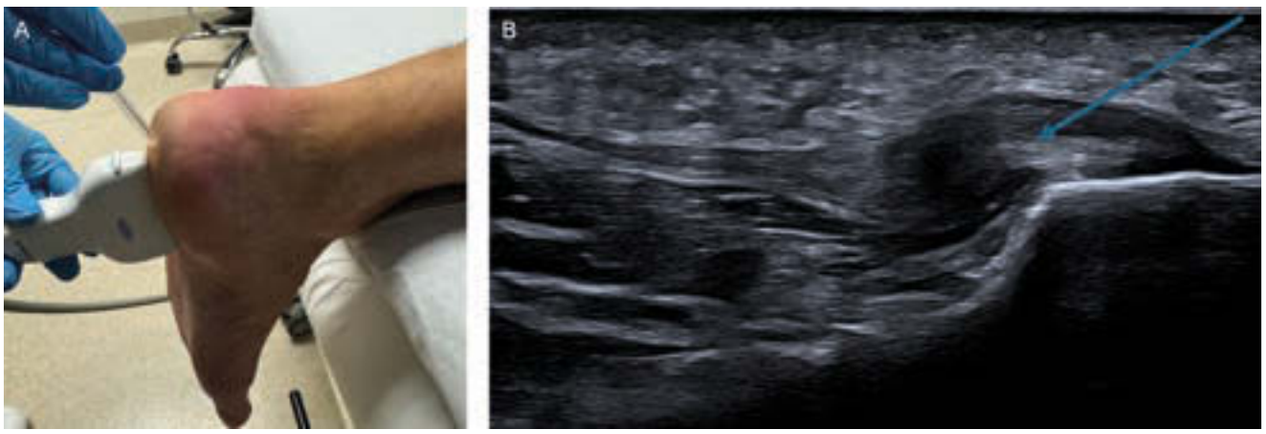


Figure 6. (A) Long axis in plane technique for injecting PRP into the plantar fascia with corresponding ultrasound image (B) with the blue arrow demonstrating the needle placement within the plantar fascia.



WHILE CLINICAL DIAGNOSIS FORMS THE FOUNDATION OF MANAGEMENT, UNDERSTANDING APPROPRIATE IMAGING INDICATIONS AND FINDINGS IS ESSENTIAL WHEN INITIAL TREATMENT FAILS OR DIAGNOSTIC UNCERTAINTY EXISTS

HYALURONIC ACID

Hyaluronic acid, a polysaccharide found in the extracellular matrix of soft connective tissues and synovial fluid, has been recently explored as a treatment for plantar fasciitis due to its viscoelastic properties, which may support extracellular matrix integrity and aid in modulating inflammatory mediators. Hyaluronic acid infiltration into the plantar fascia has been shown to provide short to medium-term pain relief and functional improvement, particularly in patients who do not respond to standard conservative therapies.[13]

EXTRACORPOREAL SHOCKWAVE THERAPY

Extracorporeal shockwave therapy delivers acoustic waves to the affected area, providing neovascularization and tissue healing. This is particularly effective for recalcitrant plantar fasciitis, with success rates of 60-80% after 3-4 months. While generally safe, minor side effects such as bruising or transient pain may occur.[14]

SURGERY

Surgery is reserved for the small minority of patients with disabling symptoms persisting beyond 6-12 months despite comprehensive non-operative care, and includes both open and endoscopic partial plantar fasciotomy.[15]

CONCLUSION

Plantar fasciitis remains a common and often challenging condition encountered in primary care. While clinical diagnosis forms the foundation of management, understanding appropriate imaging indications and findings is essential when initial treatment fails or diagnostic uncertainty exists. Conservative therapies, particularly plantar fascia-specific stretching, should form the cornerstone of initial management. Advanced treatments should be reserved for recalcitrant cases, with ultrasound guidance offering a safe and accurate approach for both corticosteroid and PRP treatments. By adopting an evidence-based stepwise approach and maintaining realistic patient expectations, most cases can be effectively managed in the primary care setting whilst always considering the need to seek specialist input for more complex presentations.

REFERENCES

1. Narvaez JA, Narvaez J, Ortega R, et al. Painful heel: MR imaging findings. *Radiographics* 2000;20(2):333-352.
2. Theodorou DJ, Theodorou SJ, Kakitsubata Y, et al. Plantar fasciitis and fascial rupture: MR imaging findings in 26 patients supplemented with anatomic data in cadavers. *Radiographics* 2000;20:S181-S197.
3. Latt D, Jaffe DE, Tang Y, et al. Evaluation and treatment of chronic plantar fasciitis. *Foot and Ankle Orthopaedics* 2020;5(1):1-11.
4. Buchbinder R. Clinical practice. Plantar fasciitis. *New England Journal of Medicine* 2004;350(21):2159-2166.
5. Lemont H, Ammirati KM, Usen N. Plantar Fasciitis: a degenerative process (fasciosis) without inflammation. *Journal of the American Podiatry medical Association* 2003;93(3):234-237.
6. Riddle DL, Pulisic M, Pidcock P, et al. Diagnostic criteria for plantar fasciitis: results of a Delphi process. *Journal of Foot and Ankle Surgery* 2003;42(5):241-249.
7. McMillan AG, Landorf KB, Barrett JT, et al. Diagnostic imaging for plantar heel pain: a systematic review and meta-analysis. *Journal of Foot and Ankle Research* 2002;5(1):32.
8. Rosenberg S, Beltran J, Bencardino JT. MR Imaging of the ankle and foot. *Radiographics* 2000;20(90001):153S-179.
9. Yu JS, Goodwin C, Raby N, et al. Plantar fasciitis: findings at MR imaging, US and radiography. *Radiology* 1996;201(2):415-419.
10. Sabir AJ, Demirlenk S, Yagci B, et al. Clinical diagnostic value of diagnostic ultrasonography and magnetic resonance imaging in plantar fasciitis. *Diagnostic Interventional Radiology* 2005;11(3):123-127.
11. DiGiovanni BF, Nawocsenski DA, Lintal ME, et al. Tissue specific plantar fascia-stretching exercise enhances outcomes in patients with chronic heel pain. A prospective, randomized study. *Journal of Bone and Joint Surgery* 2003;85:1270-1277.
12. Monto RR. Platelet-rich plasma efficacy versus corticosteroid injection treatment for chronic severe plantar fasciitis. *Foot Ankle International* 2014;35(4):313-318.
13. Raeissadat, SA, Nouri F, Darvish M, et al. Ultrasound-guided injection of high molecular weight hyaluronic acid versus corticosteroid in management of plantar fasciitis: a 24-week randomized clinical trial. *Journal of Pain Research* 2020;13:109-121.
14. Lou J, Wang S, Liu S, et al. Effectiveness of extracorporeal shock wave therapy without local anaesthesia in patients with recalcitrant plantar fasciitis: a meta-analysis of randomized controlled trials. *American Journal of Physical Medicine and Rehabilitation* 2017;96(8):529-534.
15. Feng Sm, Song RL, Wang AG, et al. Endoscopic partial plantar fasciotomy via 2 medial portals vs mini-open procedure for refractory plantar fasciitis. *Foot Ankle International* 2021;42(4):458-463.

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