Diabetic Dyslipidaemia in Gozo

Association of Glycaemic Control with Dyslipidaemic Patterns and Lipid Target Achievement in Type 2 Diabetics

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Abstract

Purpose:
To determine the frequency with which Type II Diabetes Mellitus (T2DM) patients managed in a primary care setting in the Gozitan community achieved American Diabetes Association (ADA) treatment goals for lipids and whether this was affected by the degree of glycaemic control.

Methods:
A cross-sectional study of 215 randomly selected T2DM patients treated on a primary care level was conducted. Fasting venous blood samples were collected from all patients and analysed for HbA1c, FBG, TChol, HDL and LDL (Friedewald equation). Patients were subdivided into three groups according to glycaemic control: {HbA1c < 7% (Good); 7-8% (Satisfactory); >8% (Poor)}. Amongst the three glycaemic control groups, differences in mean lipid levels were evaluated by one-way analysis of variance (ANOVA), and differences in ADA lipid target achievement by Chi squared testing.

Results:
Amongst the three glycaemic control groups, there were significant differences: in all the mean lipid levels (TChol, p<0.004; Tri, p<0.001; HDL, p<0.04; LDL, p<0.004) and lipid target achievement for Tchol (p<0.03); Tri (p<0.001); HDL (p<0.05). Frequency of ADA target achievements were: HbA1c (33.9%), TChol (58.6%), Tri (67.9%), HDL(66%), LDL (40%). Frequency of targets at goal: (none = 9.3%; 1 = 16.7%; 2 = 29.3%; 3 = 21.4%; all 4 = 23.3%).

Conclusion:
Better glycaemic control is associated with a significantly better lipid profile for each of the lipid components. The magnitude of this association was sufficient to influence achievement of all individual ADA lipid goals except that for LDL.

Introduction

Background
Gozo forms part of the Maltese Archipelago in the Mediterranean Sea. Diabetic rates of the Maltese population are amongst the highest in Europe(1) with 10% suffering from diabetes as compared to 2-3% of their European neighbours.

Overview of Literature
Lipid abnormalities affect 70-97% of diabetics(2). Diabetic dyslipidaemia is characterised by a triad of lipid abnormalities including raised Triglycerides (Tri), low High Density Lipoprotein (HDL) and a predominance of the highly atherogenic small dense form of Low Density Lipoprotein (LDL)(3). There is conclusive evidence that optimal glycaemic control is central to the management of diabetes and the prevention of long-term diabetes-related complications, both micro- and macro-vascular disease(4,5). Impaired lipid metabolism resulting from uncontrolled hyperglycaemia has been implicated in such complications. There has not been a study analysing whether the degree of glycaemic control has sufficient influence on lipid levels to significantly affect the degree of American Diabetes Association (ADA) lipid goal achievement.

ADA Recommended Targets
To improve diabetic control and prevent diabetic complications, the ADA(6) defined the following lipid treatment goals for physicians managing patients with diabetes mellitus: Total Cholesterol (TChol) \(<=5.2\ \text{mmol/l}; \text{LDL} \(<=2.6\ \text{mmol/l}; \text{HDL} >1.1 \ 5 \ \text{mmol/l}; \text{Tri}

Key Words
Type 2 Diabetes Mellitus; Glycaemic control; Diabetic Dyslipidaemia, American Diabetes Association, Primary Care.
<1.7 mmol/l; and Haemoglobin A1c (HbA1c) <7 %.

The ADA recommended goals were adopted by the study as they have been tailored specifically for diabetic patients, target all the individual lipid components, and already encompass many of the anticipated changes taking place within the European guidelines.

**Hypothesis and Study Objectives**

The frequency with which T2DM patients are able to attain recommended treatment goals in a primary care setting in Gozo remains to be established. Such data is especially important to primary care physicians who are responsible for providing the bulk of this service.

In T2DM patients, the state of insulin resistance impairs the body’s ability to sense glucose in the circulation and consequently leads to a compensatory release of free fatty acids (FFA) from adipose tissue into the bloodstream\(^1\). A high portal FFA concentration has undesirable effects on the liver resulting in hepatic insulin resistance (lipotoxicity), hyperinsulinaemia, hyperglycaemia and dyslipidaemia.

The results of several studies\(^2,9,10\) reflect a causal link between the degree of glycaemic control as a major influence on the level of dyslipidaemia and accelerated atherosclerosis as the ultimate end point. It is postulated that patients with better glycaemic control have a more favourable lipid profile than their counterparts and therefore a better chance of achieving ADA recommended targets.

A cross-sectional study was conducted to determine the frequency with which patients with T2DM managed in a primary care setting in Gozo are achieving ADA treatment goals for lipids and to determine whether the degree of glycaemic control as measured through HbA1c is associated with ADA lipid goal achievement.

The primary objectives of the study were to ascertain:

1. Whether the serum lipid profile in T2DM patients varies significantly amongst the three glycaemic control groups.
2. Whether the three glycaemic control groups have significantly different ADA lipid target achievement rates.
3. The frequency of attainment of ADA recommended lipid targets by T2DM patients in the sample population.
4. The prevailing patterns of dyslipidaemia in T2DM patients living in Gozo.

**Methodology**

**Methods / Procedure**

A cross-sectional study was conducted on 215 T2DM patients attending the Gozo Health Centre and Diabetic Outpatient clinic. The study was reviewed and approved by the local research ethics committee and patients gave informed consent. The participants were randomly selected from diabetic registers held at the above institutions using a list of computer generated random numbers. Sample size was determined by power analysis based on a power value of 0.90 and a significance level of 0.05.

The inclusion criteria for the study were:

- Patient type: diagnosed as suffering from T2DM as defined by the WHO (2007) criteria\(^1\).
- Age: between 20 to 80 years of age.
- Treatment: stabilised on same lipid-lowering therapy for ≥ 3 months.
- Location: residing in Gozo for the past 12 months.

Patients pertaining to any of the following criteria were excluded:

- Refusing informed consent
- Myocardial infarction, General anaesthesia, or major trauma within 12 weeks prior to enrollment
- Pregnant or breast feeding mothers ≤ 6 months post partum
- Haemolytic disease or significant blood loss
- Renal impairment
- Alcoholism
- On HIV medication, estrogen treatment or taking diuretics.

Recruitment of the participants and data collection took place over a 12 week period extending from September 2007 to November 2007 to avoid major festive activities which could have influenced the study results.

A data input form was completed for each participant consisting of 4 main sections: demographic details, medical history, clinical parameters and clinical lab results.

The medical history section consisted of the participant’s drug history, past medical history and relevant family history relating to diabetic/cardiovascular disease in first degree relatives. Relevant diabetes-related complications were abstracted from the patient’s medical record. The patient’s drug history including diabetic, lipid lowering and cardiovascular risk-reduction medications were also documented.
The clinical parameter section included measurement of the patient's blood pressure and body mass index (BMI). Measurement techniques were standardized and calibrated instruments used.

Venous blood samples were collected after an overnight 12-hour fast using a closed vacutainer technique and processed the same day at the Gozo General Hospital. The sera were analysed for HbA1c, fasting blood glucose (FBG), Tchol, Tri, HDL and LDL (calculated by Friedewald's equation).

Inter-laboratory and inter-method variability was avoided by having all blood samples analysed at the same quality controlled lab and using the same equipment.

The study participants were subdivided into three groups according to their degree of glycemic control as indicated by their HbA1c level. A value of <7% indicated good glycemic control, a value between 7% and 8% indicated satisfactory control, and a value >8% indicated poor glycemic control.

### Table 1: Overall study results.

<table>
<thead>
<tr>
<th>REMARK</th>
<th>TOTAL</th>
<th>MALES</th>
<th>FEMALES</th>
<th>P A R T I C I P A N T S N O T A T D A G A L</th>
<th>T C H O L</th>
<th>T R I</th>
<th>H D L</th>
<th>L D L</th>
<th>B W S</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (mean, SD, range)</td>
<td>65.9 ± 9.8 to 80</td>
<td>81 ± 8.4 to 86</td>
<td>67.8 ± 8.3 to 86</td>
<td>215</td>
<td>199</td>
<td>167</td>
<td>203</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>109 80.7%</td>
<td>106 84.3%</td>
<td>217</td>
<td>199</td>
<td>167</td>
<td>203</td>
<td>33</td>
<td></td>
<td></td>
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<tr>
<td>Glucose</td>
<td>127 ± 15</td>
<td>186 ± 14</td>
<td>137 ± 16</td>
<td>217</td>
<td>199</td>
<td>167</td>
<td>203</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>78 ± 8</td>
<td>95 ± 9</td>
<td>71 ± 7</td>
<td>217</td>
<td>199</td>
<td>167</td>
<td>203</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Weight kg</td>
<td>72.7 ± 11.8</td>
<td>86 ± 10</td>
<td>61 ± 9</td>
<td>217</td>
<td>199</td>
<td>167</td>
<td>203</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>30.4 ± 4.7</td>
<td>30.6 ± 4.8</td>
<td>30.3 ± 4.7</td>
<td>217</td>
<td>199</td>
<td>167</td>
<td>203</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>CUNCAW I</td>
<td>83 ± 13</td>
<td>90 ± 11</td>
<td>76 ± 14</td>
<td>217</td>
<td>199</td>
<td>167</td>
<td>203</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>VOLUME 18</td>
<td>57 ± 11</td>
<td>65 ± 12</td>
<td>55 ± 11</td>
<td>217</td>
<td>199</td>
<td>167</td>
<td>203</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Light Hwy</td>
<td>60 ± 15</td>
<td>68 ± 16</td>
<td>55 ± 15</td>
<td>217</td>
<td>199</td>
<td>167</td>
<td>203</td>
<td>33</td>
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</tbody>
</table>

### Statistical Analysis

The data was evaluated by SPSS v.10 statistical package. Missing values were excluded from the analysis.

### Descriptive Statistics

Descriptive statistics were performed to compute means, standard deviations, frequencies, and percentages for the demographic variables and for the lipid, blood pressure, body mass index, and HbA1c variables.

### Inferential Statistics

Pearson's correlation test was performed to examine various correlations.

The effect of glycemic control on the mean of various parameters was evaluated by one-way analysis of variance (ANOVA). Values of p<0.05 were considered statistically significant.
Chi squared testing was employed to analyse ADA lipid target achievement (nominal binary outcome variables) amongst the three glycaemic control groups.

**Results & Data Analysis**

**Overall mean results**

The study data are summarized in table 1. A total of 109 males and 106 females took part in the study with an overall mean age of 66 (+/- 10) years ranging between 34 and 80 years. Overall, study participants were obese with an average BMI of 30.4kg/m² ranging from 18.2 to 53.1 kg/m² with a mean blood pressure of 137/78 mmHg. Glycaemic control was found to be narrowly satisfactory with a mean (SD) HbA1c of 7.98% (+/-2.00) ranging from 4.5 to 14.4% whilst mean (SD) FBG was 9.8 (+/-3.7) mmol/l. The overall mean (SD) lipid levels of all the study participants were found to be as follows: TChol 5.0mmol/l (+/-2.3), Tri 1.6 mmol/l (+/-0.9), HDL 1.3 mmol/l (+/-0.3) and LDL 3.0 mmol/l (+/-0.9).

Analysis using Pearson’s correlation coefficient showed that both HbA1c and FBG respectively exhibited statistically significant linear correlations with each of the lipid components: Tchol 0.24 (p<0.001), 0.20 (p<0.001); Tri 0.19 (p<0.002), 0.21 (p<0.001); HDL -0.13 (p<0.029),
The percentage of participants achieving ADA recommended targets for HbA1c, TC, Tri, HDL, and LDL are depicted in Fig. 1.

Results after Stratification into three Glycaemic Control Groups

Glycaemic Characteristics

The three glycaemic control groups were similarly matched with regards to age, gender distribution, BMI and proportion of patients on lipid lowering treatment. The distribution of patients amongst the glycaemic control groups was as follows: 34.0% had Good glycaemic control, 26.5% achieved Satisfactory glycaemic control, and the largest percentage 39.5% had Poor glycaemic control. Their respective mean HbA1c levels were 6.1%, 7.5% and 9.9% respectively.

Mean Lipid Values

The mean lipid values in the glycaemic control groups are depicted in the figure below. The difference in lipid levels between the three groups were significant for all of the lipoproteins.

ADA Lipid Target Achievement & Lipid Profile Pattern

The three glycaemic control groups showed different degrees of ADA lipid target achievement as demonstrated in Fig. 3.

The number and frequency of lipid goals achieved amongst the three glycaemic control groups is depicted in Fig. 4.

The good glycaemic control group had the highest percentage of patients (31.5%) achieving all four ADA lipid targets. The satisfactory glycaemic control group fared the worst in ADA lipid target achievement with 15.8% of the patients in this group not achieving any of the ADA lipid targets. The lipid profile showed that 76.7% of the patients had at least one lipid value outside the ADA recommended clinical target level whilst 9.3% did not succeed in achieving any of the goals.

The commonest ADA lipid target achievement pattern in all three glycaemic control groups is a lipid profile with Tri and HDL both at goal.

Discussion & Interpretation of Results

HbA1c correlated well with each of the lipid components. The magnitude of impaired glycaemic control as defined by the three different cutoff values of HbA1c was proportionally related with dyslipidaemia in terms of significantly higher total cholesterol, triglycerides, and LDL levels, and lower HDL levels. This was also reflected in ADA lipid goal achievements. Except for LDL, all ADA lipid goal achievement rates were higher in those with better glycaemic control. There was a clear gap between goals put forth in guidelines and outcomes achieved in primary care\(^{(12)}\). Furthermore, this study gave an unprecedented insight into the local scenario of diabetic management in the Gozitan community highlighting that LDL goals were not adequately being met as compared with other European countries.
**Aim 1:**
**Differences in Lipid Profile in Type 2 Diabetes Mellitus Patients According to the Degree of Glycaemic Control**

Glycaemic control was associated with significant differences amongst all the lipid components analysed. The better the glycaemic control, the better the associated mean lipid levels (fig. 2). Pearson’s analysis demonstrated a highly significant direct correlation between HbA1c and each of the individual lipid levels apart from HDL which similarly showed a directly inverse correlation. Glycaemic control plays an important and significant role in influencing dyslipidaemic levels in T2DM patients and can be a potentially useful tool to improve all the components of diabetic dyslipidaemia. This has practical importance for those components for which there is limited pharmacological assistance such as HDL and Tri. The methods used to achieve glycaemic control can have differential effects on lipid levels beyond their effects on glucose metabolism. This data expands the clinical applicability of HbA1c not only as a reliable biomarker of glycaemic control, but also as an indirect indicator of serum lipid profile in T2DM patients. Patients with impaired glycaemic control have a higher tendency towards having a deranged lipid profile and should be thoroughly assessed for dyslipidaemia and associated complications.

**Aims 2 & 3:**
**Association of Glycaemic Control with Ada Lipid Goal Achievement & Frequency of Ada Goal Achievement**

Although the magnitude of the effect of glycaemic control on lipid profile has been described to be of limited value by some authors, the current study corroborates what Wagner et al. had concluded from a prospective longitudinal intervention study in that glycaemic optimisation is a useful tool to improve the components of diabetic dyslipidaemia whereby although the effect is individually modest they are globally significant. As seen in Fig. 3, the better the degree of glycaemic control, the higher the achievement rates of all four ADA lipid targets simultaneously (p<0.05). Similarly, with improved glycaemic control, there was a significant decrease in the proportion of patients with none of the lipid targets at goal (p<0.01). When the effect on individual lipid target achievement was analysed, better glycaemic control was associated with significantly better ADA goal achievements for TChol (p<0.03) and Tri (p<0.001). The magnitude of this effect appeared to be insufficient to produce a significant increase in HDL and LDL ADA target achievement.

As this may have been partially due to the overwhelming influence of lipid lowering medications on these parameters, patients in the three glycaemic control groups were further subdivided into those on and those not on lipid lowering treatment and the individual lipid profiles analysed to differentiate any pharmacological influence. Chi Squared analysis revealed that in the non-lipid treatment sub-groups, improved glycaemic control was associated with significant differences in HDL goal achievement (5.9, p<0.05) and Tri goal achievement (17.9, p<0.001), but did not influence LDL goal achievement (1.4, p>0.05).

This may be accounted for due to LDL targets being the most stringent and difficult to achieve as well as LDL levels are mainly altered qualitatively rather than quantitatively in diabetic dyslipidaemia. These results are consistent with findings by Erdman et al. supporting the need for lipid modifying agents to be introduced early in the management of T2DM patients with high LDL levels.

The study revealed that better glycaemic control was associated with higher frequencies of ADA lipid goal achievement. The commonest lipid pattern affecting T2DM patients in the Gozitan community was the achievement of two ADA lipid goals (29.3%) with the most frequent lipid combination being a combination of Tri and HDL both at goal (16.7%). This pattern was most prevalent in the good and poor glycaemic control groups. Standard approaches to managing diabetes will likely benefit HDL and Tri levels even without use of lipid-directed medications.

**AIM 4:**
**Overall Results - The Prevailing Patterns of Diabetic Dyslipidaemia in Type 2 Diabetic Patients in Gozo in Comparison with other Studies**

The current study portrayed the local diabetic dyslipidaemia scenario. Overall, the average lipid levels were within recommended ADA lipid targets except for LDL. More than 50% of the T2DM patients studied had achieved ADA recommended treatment goals for TChol, Tri and HDL. Tri levels had the highest ADA goal achievement whilst LDL goal was the most difficult to achieve. Only 40% of patients managed to achieve the ADA recommended treatment goal for LDL. This is low when compared with other European countries which had a 51% achievement rate according to the EUROASPIRE II study. When these values are compared with the proportion of patients...
reaching glycaemic goal (33.95%), one finds that there is a higher proportion of lipid target achievement than HbA1c achievement (see Fig. 1). Although only 34% of the study patients were within the established ADA target for glycaemic control (HbA1c<7%), it is comparable to international figures. Studies by the American Diabetes Association[18], The European Diabetes Policy Group[19] and the Canadian Diabetes Association[20] highlighted that over 60% of people with T2DM are still not achieving recommended glycaemic goals despite stringent guidelines for diabetes management.

Limitations of the Study
- Pertains to a single point in time and limited to community practice settings.
- Physicians may have been following different guideline recommendations.

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- Pertains to a single point in time and limited to community practice settings.
- Physicians may have been following different guideline recommendations.
- No data on patient compliance and on non-pharmacological therapies pursued by patients.

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References