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RESEARCH ARTICLE

The interaction of dyslipidaemia with glycaemia in an adult population study

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Abstract

Purpose Individuals with dysglycaemic are prone to dyslipidaemia. Understanding the dyslipidaemic status of dysglycaemic individuals is essential for monitoring and early prevention. The aim was to assess the control of lipidaemia by glycaemic status in a representative adult population.

Methods A retrospective health examination survey was performed on a sample of adults ($n = 3947$) in Malta in 2014–6. Sociodemographic data, biochemistry blood tests and anthropometric measurements were gathered. Statistical analysis was performed to evaluate the lipidaemic status and its control across the glycaemic spectrum (normoglycemic, impaired fasting glucose individuals, new diabetics and known diabetics).

Results The prevalence of *uncontrolled dyslipidaemi*a was 7.75% (CI 95%: 6.69–8.63), among whom 6.97% (CI 95%: 6.21–7.81) were naïve dyslipidaemic. A progressive elevation in both LDL-C and total cholesterol but not triglycerides was present among *uncontrolled dyslipidaemi*a individuals across the glycaemic spectrum. *Global dyslipidaemia* was present in 19.26% (CI 95%: 18.05–20.52) of the total general population and in 46.59% (CI 95%: 40.49–52.69%) of known diabetics. Most individuals irrespective of lipid status were normoglycaemic.

Conclusions Dyslipidaemia occurs in the presence of insulin resistance. Dyslipidaemia predominated in the normoglycaemic state irrespective of statins use, indicating the need to manage dyslipidaemia prior to dysglycaemia.

Keywords Hyperlipidaemia · Diabetes mellitus, type 2 · Insulin resistance, policy · Epidemiology · Malta

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Introduction

Understanding the dyslipidaemic status and its metabolic correlations at population level is essential for monitoring of health status, planning and evaluating healthcare. Dyslipidaemia is the presentation of combined elevation of low-density lipoprotein cholesterol (LDL-C) level and an elevated triglyceride level and a decreased high-density lipoprotein cholesterol (HDL-C) level [1]. This is a common occurrence in dysglycaemic individuals, especially among those with an established diabetes mellitus type 2, also known as diabetic dyslipidaemia [2]. Furthermore, dyslipidaemia is a well-established contributor to the development of cardiovascular disease especially in dysglycaemic individuals [2, 3]. Individuals suffering from diabetes mellitus have been reported to have a 2- to 4-fold increased risk for the developing of cardiovascular disease. In fact, diabetes has been identified as a coronary artery disease risk factor [4, 5].

Individuals with diabetes tend to lose the ability to metabolise lipids and lipoproteins, increasing the risk of elevated low-density lipoprotein (LCL-C), elevated triglycerides and a

decreased level of high-density lipoprotein (HDL-C) [6]. The diabetic LDL-C particle tend to be smaller and denser due to the simultaneous presence of high triglyceride levels. This contributes to the documented "atherogenic lipid pattern", which is present in both pre-diabetic and diabetic individuals (impaired fasting glucose and impaired glucose tolerance) [7, 8]. These smaller, denser LDL-C particles have greater ability to penetrate into the blood vessels, thereby potentiating the risk for thrombus formation [9]. A reduction of 1 mmol/L of the mean LDL-C plasma level at population level is thought to contribute to a 21% risk reduction in cardiovascular mortality [10, 11].

The most commonly used lipid-lowering medications are statins. Statins block the 2-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) conversion to mevalonic acid and therefore limit cholesterol synthesis [12]. In turn, lower hepatic cholesterol levels result, leading to an increase in low-density lipoprotein (LDL)-receptor expression in hepatocytes. This leads to an enhanced LDL-particle clearance from the blood [13]. Statins also act on reducing the triglyceride levels whilst increasing the high-density lipoprotein [12, 14].

The Mediterranean Island of Malta has been reported to have high diabetes mellitus type 2, obesity and hypertension prevalence rates when compared to other European countries [15–18]. This makes the adult population of Malta an ideal cohort in which to analyse the effects of glycaemia on lipidaemic status. Furthermore, considering that the total population of Malta is less than half a million and that the Maltese Islands are small (316Km [2]), the short distances between towns made it feasible for a nationally representative health examination survey to be conducted with all participants undergoing fasting lipid profile testing. Commonly, epidemiological studies are unable to undergo such an extensive examination at a population level [3].

The aim of this study was to assess the glycaemic status of the population in relation to their lipidaemia control with or without the use of statins, while establishing the prevalence of *uncontrolled* and *global* dyslipidaemia among the high-risk Maltese population. The hypothesis was that as the glycaemic spectrum shifts from normoglycaemia to full-blown diabetes mellitus, the lipid profile would become more dyslipidaemic without the use of statins, while it would stay more within the normal range for those on statins. Such data can facilitate a comparative review by neighbouring Mediterranean countries as well as among other high diabetes prevalence countries. The data will aid in the identification of dyslipidaemic changes at population level which may relate to the onset of cardiometabolic complications and to understand the relationships between dyslipidaemia and dysglycaemia.

Method

A retrospective cross-sectional survey on diabetes mellitus type 2 was conducted between November 2014 and January 2016 under the auspices of the University of Malta. The detailed study protocol was described elsewhere [19]. In summary, a nationally representative health examination survey was performed on a randomised, stratified sample. Stratification was affected by age (18–70 years), gender and town, with individuals selected from across all towns within the Maltese Islands. The sample population under study represented approximately 1% of each town's adult population. Blood tests performed as part of the health survey included fasting blood glucose (FBG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and total cholesterol (TC). Informed written consent was obtained from every participant. Ethical and data protection approvals were granted from the University of Malta Research Ethical Committee (UREC) and the Information and Data protection national commissioner respectively.

The segment of the study population obtaining a dyslipidaemic status (high LDL-C + high triglycerides + low HDL-C levels) at the time of the health examination survey was labeled as *uncontrolled dyslipidaemia.* The dyslipidaemia status was defined as an elevated LDL-C of ≥3 mmol/l, an elevated triglyceride (TG) level of ≥1.69 mmol/L and a low HDL-C level of ≤1.03 mmol/L for males and ≤ 1.29 mmol/L for females [5, 20, 21]. The label of *global dyslipidaemia* was given to the proportion of the study population that reported to be on statin medication irrespective of current measured lipid profile, in combination with those participants that were found to have dyslipidaemia during the health examination survey but were not on statin medication. Therefore, this population (global dyslipidaemia) was hypothesized to represent the whole Maltese dyslipidaemic population with potential atherogenic changes and susceptibility to dysglycaemia.

The study population was subdivided into four glucose regulatory subgroups, namely normoglycaemia, impaired fasting glucose (IFG), newly diagnosed diabetes mellitus (NDM) and previously known diabetes mellitus (KDM) subgroups. This was performed in order to represent a continuum in the transition from normal to disordered glucose metabolism, which enabled a more accurate biochemical analyses across the glucose transition. The subdivision was based on the fasting blood glucose results obtained during the health examination survey while incorporating any self-reported history of diabetes mellitus. Those participants obtaining a fasting blood glucose (FBG) level between 5.6–6.9 mmol/L and not reporting to be on oral hypoglycaemic agents were labeled as *Impaired Fasting Glucose* (IFG). All IFG individuals reported to have not been aware of their dysglycaemia before the health examination survey. Those participants with a FBG > =7 mmol/L were labeled as *Newly diagnosed diabetes mellitus* (NDM), provided they were not previously diagnosed as diabetics or were on oral hypoglycaemic agents [22]. Identifying newly diagnosed diabetics following a single fasting blood glucose reading is a common practice in population-based health examination surveys [23]. The

participants with a previous history of diabetes mellitus or on oral hypoglycemic agents, irrespective of their measured fasting plasma glucose, were labeled as cases of *known diabetes mellitus* (KDM). Those individuals who did not fall within these glucose dysglycaemic categories were considered as having normoglycaemia.

The Kolmogorov-Smirnov test for normality confirmed that the blood test measurements for the population were not normally distributed. Statistical analyses using non-parametric tests were performed using IBM SPSS version 21. The median and interquartile ranges (IQR) were calculated for the lipid profile variables within each of the four-glycaemic subgroups. The Kruskal-Wallis test was performed to establish any significant differences between each lipid profile variable and the corresponding glycaemic subgroup within the different dyslipidaemic populations (uncontrolled and global). Pairwise comparisons (Dunn's test) between the four-glycaemic subgroups for each dyslipidaemic population were performed.

Results

A total sample population of 3947 adults was included in the study after weighting for non-responders (response rate of 49%, $p = <0.05$). The prevalence of high LDL-C levels was 51.25% (CI 95%: 49.69–52.81), that of high triglyceride levels was 15.05% (CI 95%: 13.97–16.20) and that of high cholesterol levels was 52.31% (CI 95%: 49.19–52.31) for the entire population. The prevalence of *uncontrolled dyslipidaemi*a (high LDL-C + high TG + Low HDL-C) at the point of the study was of 7.75% (CI 95%: 6.69–8.63). The *uncontrolled dyslipidaemi*a population was composed of naïve dyslipidaemic individuals ($n = 275$) and individuals reported to be on statins ($n = 485$) yet still with uncontrolled dyslipidaemia during the examination ($n = 31$). Thus, the 7.75% of prevalent current uncontrolled dyslipidemia consisted of a proportion with naïve dyslipidaemia - 6.97% (CI 95%: 6.21–7.81) and a proportion of those with known dyslipidaemia, on statins and yet uncontrolled - 0.79% (CI 95%: 0.55–1.12). The naïve dyslipidaemia sub-population was predominantly male (76.73% CI 95%: 71.37–81.35) aged between 30 and 70 years.

Considering that the *uncontrolled dyslipidaemi*a population was predominantly composed of naïve dyslipidaemic individuals, it was hypothesized that this population represented the uncontrolled lipidaemia adult population of Malta who remained mostly without dyslipidaemic awareness and without the effect of statins.

Participants on statins may have been taking these due to either a known dyslipidaemic status or else had been started as a preventive measure following certain conditions such as cardiovascular disease or at onset of diabetes mellitus [24]. Regrettably, data pertaining to the reason the participants were on statins was not available.

The *global dyslipidaemia* population contributed to 19.26% (CI 95%: 18.05–20.52) of the total general population. The *global dyslipidaemic* population was considered as representative of the total adult population of Malta with a dyslipidaemic status with or without statin medication at population level. This *global dyslipidaemia* population consisted of the combination of individuals that were already on statin treatment ($n = 485$, out of which $n = 31$ had uncontrolled dyslipidaemia on examination) in addition to naïve cases ($n = 275$).

Global dyslipidaemia was found to be present in 46.59% (CI 95%: 40.49–52.69%) of this study population's known diabetes sub-population.

Both populations (*uncontrolled* and *global* dyslipidaemia) were sub-categorised according to their glycaemic status that was established during the health examination survey, as seen in Table 1. For both the dyslipidaemic populations (*uncontrolled* and *global*), the majority of the individuals exhibited a normoglycaemic status (FBG <5.6 mmol/L with no history of diabetes) with a female predominance, followed by impaired fasting glucose (IFG) with a male predominance. As expected, the newly diagnosed diabetic (NDM) subgroup exhibited a slightly higher proportion with *uncontrolled dyslipidaemia* when compared to previously known diabetics (KDM). This follows the standard practice where statin therapy is initiated with the onset of diabetes mellitus [25]. This finding contrasted with the *global dyslipidaemia sub*-population, where the KDM sub-group contributed a higher proportion when compared to the NDM subgroup.

Table 2 illustrates the reported statin use across the different glycaemic status sub-groups in relation to the two dyslipidaemic (*uncontrolled* and *global*) populations while being contrasted with the general population. A progressive steady increase in statin use was observed within the general population across the glycaemic spectrum from normoglycaemia to previously known diabetes mellitus. However, on evaluating those with *uncontrolled dyslipidaemia* status, the IFG subgroup individuals reported a predominance for statin medication. Interestingly 2.94% (CI 95%: 1.47–5.58) of the *uncontrolled dyslipidaemic* population was cognizant of their diabetes mellitus status and were already on statins, yet still had uncontrolled dyslipidaemia. The highest reported statin use within the *global dyslipidaemic* population was amongst the normoglycaemic sub-group, which coincides with the established fact that the *global dyslipidaemic* population was predominated by the normoglycaemic status.

Uncontrolled dyslipidaemia population

The median lipid profile components of the *uncontrolled dyslipidaemia* population were evaluated across the

Table 1 Summarizes the different lipid status sub-population according to their glycaemic status

Population		Glycaemic status			
		Normoglycemic	IFG	NDM	KDM
Uncontrolled dyslipidaemia ($n = 306$)	Total	49.35%	32.03%	9.48%	9.15%
	Female ($n = 77$)	61.04%	28.57%	2.60%	7.79%
	Male ($n = 229$)	45.41%	33.19%	11.79%	9.61%
Global dyslipidaemia* ($n = 760$)	Total	40.39%	27.37%	10.39%	21.84%
	Female ($n = 285$)	46.32%	26.32%	7.02%	20.35%
	Male ($n = 475$)	36.84%	28.00%	12.42%	22.74%
Normal lipidaemia** ($n = 1550$)	Total	75.74%	1.61%	7.16%	15.48%
	Female ($n = 824$)	81.92%	1.21%	5.10%	11.77%
	Male ($n = 726$)	68.73%	2.07%	9.50%	19.70%
General ($n = 3947$)	Total	66.28%	23.44%	4.03%	6.31%
	Female ($n = 1949$)	74.50%	18.57%	2.82%	4.16%
	Male ($n = 1998$)	58.26%	28.18%	5.21%	8.41%

*Global dyslipidaemia – the combination of uncontrolled dyslipidemia found during health examination, controlled dyslipidaemia found during health examination but on reported statin treatment

**Normal LDL-C + Triglycerides + HDL-C

IFG, Impaired fasting glucose; *NDM*, Newly diagnosed diabetes mellitus; *KDM*, Previously known diabetes mellitus

glycaemic transition, from normoglycaemia to full-blown known diabetes mellitus, as seen in Table 3. As expected the new DM sub-group exhibited a significantly higher LDL-C and total cholesterol levels when compared to all other glycaemic status groups (except when total cholesterol was compared to normoglycaemic sub-group). There was no significant difference between the lipid profile components of the normoglycaemic and the impaired fasting glucose sub-categories. On further sub-analysing the *uncontrolled dyslipidaemia* population by gender, the female population showed a tendency for higher lipid profile components when compared to the male proportion within the normoglycaemic (except for triglycerides), NDM and KDM sub-groups, as seen in Table 4.

Global dyslipidaemia population

The median lipid profile components of the *global dyslipidaemic* population across the glycaemic status are shown in Table 5. The previously known diabetes (KDM) dyslipidaemic sub-group exhibited significantly lower LDL-C, triglycerides and total cholesterol levels when compared to normoglycaemic, IFG and newly diagnosed (NDM) sub-groups. Conversely, similarities were present across all lipid profile components between normoglycaemic, IFG and NDM dyslipidaemic sub-groups. On sub-analysing the *global dyslipidaemic* population by gender, similarities between the females and males were evident. However, across all the glycaemic spectrum females exhibited significantly higher HDL-C levels than did males, as seen in Table 6.

Uncontrolled dyslipidaemia vs. global dyslipidaemia populations

On comparing the lipid profile components of the *uncontrolled dylipidaemia* population to *the global dyslipidaemia* population, significant differences were found between the lipid profile components across all the glycaemic status sub-groups, as shown in Tables 3, 4, 5, and 6. The median LDL-C, triglycerides and total cholesterol values were significantly higher within the *uncontrolled dylipidaemia* population when compared to the *global dyslipidaemia* population. This held true also on gender stratification ($p = <0.01$ respectively). The HDL-C median levels were significantly lower within the *uncontrolled dylipidaemia* population when compared to the

Table 2 Summarises the reported statin uses across the different glycaemic status, by the different lipidaemia populations under study

Populations	Glycaemic status - reported to be on statins				Total on statin
	Normoglycemic	IFG	NDM	KDM	
Uncontrolled dyslipidaemia ($n = 306$)	1.63%	4.90%	0.65%	2.94%	10.13%
Global dyslipidaemia* ($n = 760$)	21.18%	16.45%	6.71%	19.34%	63.68%
Normal lipidaemia ($n = 1550$)	4.97%	0.77%	5.42%	2.58%	13.74%
General ($n = 3947$)	6.15%	13.51%	32.08%	59.44%	12.29%

*Global dyslipidaemia – the combination of uncontrolled dyslipidemia found during health examination, controlled dyslipidaemia found during health examination but on reported statin treatment

Table 3 Uncontrolled dyslipidaemic population median lipid profile components, by glycaemic status

	Uncontrolled dyslipidaemia										
	Normoglycemic ($n = 151$)	IFG ($n = 98$)	NDM ($n = 29$)	KDM ($n = 28$)	*Kruskal-Wallis*	*Dunn's test*					
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	p value	p value1	p value2	p value3	p value4	p value5	p value6
Age (years)	40 (18)	57 (19)	51 (19)	55 (17)	**<0.01**	**<0.01**	**0.01**	**<0.01**	1	1	1
LDL (mmol/L)	3.83 (1.09)	3.85 (1.02)	4.17 (1.52)	3.43 (0.84)	**<0.01**	1	**<0.01**	**0.01**	**<0.01**	0.08	**<0.01**
HDL (mmol/L)	1.09 (0.24)	1.02 (0.23)	1.02 (0.25)	0.98 (0.17)	**0.01**	0.17	0.16	0.06	1	1	1
Triglycerides (mmol/L)	2.16 (0.91)	2.49 (1.29)	2.20 (1.24)	2.21 (0.97)	0.18						
Total Cholesterol (mmol/L)	6.05 (1.02)	6.10 (0.96)	6.47 (1.66)	5.61 (0.89)	**<0.01**	1	0.18	**<0.01**	**0.04**	**0.01**	**<0.01**
BMI (Kg/m2)	30.80 (7.90)	30.00 (5.90)	31.10 (11.38)	29.30 (7.69)	0.84						

p value1, Normoglycaemic vs. IFG; *p value2*; Normoglycaemic vs. NDM; *p* value3, Normoglycaemic vs. KDM; *p value4*, IFG vs. NDM; *p value5*, IFG vs. KDM; *p value6*, NDM vs. KDM; *IQR*, Interquartile range; *IFG*, Impaired fasting glucose; *NDM*, Newly diagnosed diabetes mellitus; *KDM*, Known diabetes mellitus

Table 4 Uncontrolled dyslipidaemic population median lipid profile components, by glycaemic status and gender

	Normoglycaemic		*p* value*	IFG		*p* value*	NDM		*p*-value*	KDM		*p*-value*
	Female ($n = 47$) Median (IQR)	Male ($n = 104$) Median (IQR)		Female ($n = 22$) Median (IQR)	Male ($n = 76$) Median (IQR)		Female ($n = 2$) Median (IQR)	Male ($n = 27$) Median (IQR)		Female ($n = 6$) Median (IQR)	Male ($n = 22$) Median (IQR)	
Age (years)	45 (23)	40 (18)	0.99	63 (18)	55 (21)	**<0.01**	65 (10)	51 (19)	**0.01**	61 (10)	52 (17)	0.11
LDL-C (mmol/L)	4.05 (1.08)	3.76 (1.00)	**<0.01**	3.98 (1.08)	3.85 (0.95)	0.66	5.65 (0.89)	4.17 (0.92)	**0.01**	3.34 (0.21)	3.75 (0.84)	0.13
HDL-C (mmol/L)	1.13 (0.28)	1.08 (0.26)	**0.01**	1.03 (0.12)	0.99 (0.22)	0.24	1.12 (0.25)	1.02 (0.24)	**0.01**	1.29 (0.25)	0.88 (0.14)	**<0.01**
Triglycerides (mmol/L)	1.95 (0.57)	2.19 (0.86)	**<0.01**	2.42 (1.11)	2.70 (1.33)	0.60	4.49 (1.26)	2.11 (1.24)	**0.02**	2.60 (0.88)	1.80 (0.78)	**0.03**
Total Cholesterol (mmol/L)	6.40 (0.89)	5.88 (1.02)	**0.01**	6.22 (0.80)	6.06 (1.03)	0.54	8.69 (1.33)	6.47 (1.35)	**0.01**	5.69 (0.61)	5.61 (0.89)	0.14

*Mann-Whitney U test

Table 5 Global dyslipidaemic population median lipid profile components, by glycaemic status

	Global dyslipidaemia										
	Normoglycemic ($n = 307$)	IFG ($n = 208$)	NDM ($n = 79$)	KDM ($n = 166$)	*Kruskal-Wallis*	*Dunn's test*					
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	p-value	p-value1	p-value2	p-value3	p-value4	p-value5	p-value6
Age (years)	54 (24)	59 (12)	62 (14)	64 (10)	**<0.01**	**<0.01**	**<0.01**	**<0.01**	1	**0.02**	0.54
LDL (mmol/L)	3.37 (1.19)	3.32 (1.21)	3.60 (1.45)	2.47 (1.07)	**<0.01**	1	1	**<0.01**	1	**<0.01**	**<0.01**
HDL (mmol/L)	1.23 (0.47)	1.18 (0.49)	1.12 (0.48)	1.23 (0.65)	0.25						
Triglycerides (mmol/L)	1.84 (1.15)	1.77 (1.48)	1.83 (1.50)	1.35 (0.90)	**<0.01**	1	0.46	**<0.01**	0.77	**<0.01**	**<0.01**
Total Cholesterol (mmol/L)	5.63 (1.43)	5.43 (1.46)	5.47 (1.55)	4.53 (1.34)	**<0.01**	1	1	**<0.01**	**<0.01**	1	**<0.01**
BMI (Kg/m2)	28.83 (6.90)	29.61 (5.77)	31.40 (9.98)	31.05 (6.03)	**<0.01**	0.1	**<0.01**	**<0.01**	**0.05**	1	0.7

p-value1, Normoglycaemic vs. IFG; *p value2*, Normoglycaemic vs. NDM; *p value3*, Normoglycaemic vs. KDM; *p value4*, IFG vs. NDM; *p value5*, IFG vs. KDM; *p value6*, NDM vs. KDM; *IQR*, Interquartile range; *IFG*, Impaired fasting glucose; *NDM*, Newly diagnosed diabetes mellitus; *KDM*, Known diabetes mellitus

Table 6 Global dyslipidaemic population median lipid profile components, by glycaemic status and gender

	Normoglycaemic		*p*-value*	IFG		*p*-value*	NDM		*p*-value*	KDM		*p*-value*
	Female ($n = 132$) Median (IQR)	Male ($n = 175$) Median (IQR)		Female ($n = 75$) Median (IQR)	Male ($n = 133$) Median (IQR)		Female ($n = 20$) Median (IQR)	Male ($n = 59$) Median (IQR)		Female ($n = 58$) Median (IQR)	Male ($n = 108$) Median (IQR)	
Age (years)	58 (20)	51 (37)	**<0.01**	63 (10)	58 (15)	**<0.01**	64 (8)	60 (14)	**0.02**	64 (8)	64 (13)	0.92
LDL-C (mmol/L)	3.10 (1.32)	3.50 (1.10)	0.16	3.32 (1.13)	3.37 (1.23)	0.44	3.43 (1.64)	3.66 (1.14)	0.80	2.36 (0.91)	2.62 (1.18)	0.61
HDL-C (mmol/L)	1.37 (0.51)	1.13 (0.30)	**<0.01**	1.44 (0.60)	1.12 (0.31)	**<0.01**	1.47 (0.26)	1.09 (0.36)	**<0.01**	1.48 (0.44)	1.03 (0.44)	**<0.01**
Triglycerides (mmol/L)	1.46 (0.97)	1.97 (1.27)	**<0.01**	1.40 (1.23)	1.81 (1.54)	**<0.01**	1.44 (1.17)	1.85 (1.29)	0.21	1.30 (0.75)	1.46 (0.91)	0.17
Total Cholesterol (mmol/L)	5.41 (1.74)	5.66 (1.36)	0.98	5.41 (1.35)	5.50 (1.65)	0.59	5.47 (2.04)	5.48 (1.46)	0.61	4.61 (1.26)	4.48 (1.55)	0.26

*Mann-Whitney U test

global dyslipidaemia population, even after gender stratification ($p = <0.01$ respectively). Of note was the fact that the *global dyslipidaemia* population was significantly older (in years) when compared to the *uncontrolled dylipidaemia* population.

Discussion

Dyslipidemia is a physiological occurrence in the presence of insulin resistance with or without the presence of hyperglycaemia [26, 27]. Lipoprotein abnormalities typically initiate in the pre-diabetic state [28]. In our study, the highest population proportion contributing to both the *uncontrolled* and *global* dyslipidaemic populations were found to have normoglycaemic status. However, when compared, the normoglycaemic and the IFG (pre-diabetes) lipid profile components were found to be similar with both exhibiting a high triglyceride level. This may suggest underlying insulin resistance that will lead to a shift from normoglycaemia to dysglycaemia in a matter of time even though the current FBG was within the normal range. In fact, it has been reported that dysregulation of lipids indicates underlying pathophysiological abnormalities such as insulin resistance and abdominal obesity which contribute to hyperinsulinaemia. This in turn leads to hyperglycaemic status and enhances hepatic gluconeogenesis and glucose output. Furthermore, a reduction in the suppression of adipose tissue lipolysis occurs resulting in an eventual hypertriglyceridemia and reduced HDL-C levels [29]. In our study, the body mass indexes (BMI) of both the normoglycaemic and IFG sub-groups were found to have comparable obesity states, which further supports the fact that insulin resistance may have been present. It is a well-known fact that both insulin resistance and obesity are features of the metabolic syndrome that is involved in both the lipid and glucose metabolism [21, 30].

The *uncontrolled dyslipidaemia* population lipid components showed a progressive median incline across the glycaemic spectrum (Normoglycaemia-IFG vs. NDM) for both the LDL-C and total cholesterol levels but not for triglycerides. The triglyceride levels across the glycaemic spectrum, although elevated, did not show any significant changes across the glycaemic spectrum, which is not in keeping with the literature [31].

Considering that the pre-diabetic subgroup (IFG) within our study reported to have not been previously aware of their dysglycaemia; it can be hypothesized that the use of statins (within this subgroup) prior to their knowledge of dysglycaemia suggests that diabetic dyslipidaemia had already started to develop and supports the literature in that lipoprotein changes occur in the pre-diabetic state [28]. In fact, this observation was further supported by the progressive statin usage trend across the glycaemic spectrum within our study population. It is documented that as dysglycaemia appears more evident, so too does dyslipidaemia and/or related co-morbidities such as cardiovascular disease [32]. For this reason, initiating statin therapy as a preventive measure against dyslipidaemic complications is a common practice along with lifestyle management for newly diagnosed diabetics [24]. It is important to note that lower lipid profile component targets are set for certain conditions, such as in dysglycaemic individuals [5]. However, a considerable number of individuals treated with statins do not achieve the treatment goal values envisaged by physicians. This could be observed in our study, where a percentage of previously known diabetic individuals were found to have uncontrolled dyslipidaemic despite their statin medication [3]. One possible reason for the presence of uncontrolled dyslipidaemia in this group is non-adherence to medication. This is a common public health challenge with as many as 50% of patients discontinuing their medications within a year of initial prescription [33, 34]. Such practices could result in long-term complications, co-morbidities and premature mortality, which also incur additional costs to the health care system [35]. This non-adherence to medication may explain why not every previously known diabetic individual attending our study reported to be on statin medication. This follows the fact that it is of standard practice in Malta and internationally that all newly diagnosed diabetic individuals are started on lifestyle modifications followed by statin treatment [25, 36]. It appeared that within our KDM population, the males were even less adherent to their medication when compared to their female counterparts as age progressed. Conversely, non-adherence to medication was reported to be multi-factorial and gender-specific [37, 38]. However, the lack of data on the heterogeneity of statin dose among the compliant participants may have had an effect on the study's outcome.

Conclusions

Understanding the dylipidaemic pathophysiology with its early onset prior to the development of any co-morbidities, including dysglycaemia, is essential. Our study provides the evidence that dyslipidaemia predominates in normoglycaemic states irrespective of statins use, with those on statin medications having lower lipid profile components. Initiating educational outreaches to the population to undergo medical check-ups for the presence of dyslipidaemia, especially in high-risk populations, is essential. Physicians should supplement lifestyle modification with statin therapy depending on the plasma lipid profile results. Managing dyslipidaemia in its early stages, prior to the presence of dysglycaemia should be the norm according to current clinical guidelines. This could prevent co-morbidities including diabetes and cardiovascular diseases from developing, as well as lowering related mortality rates.

Study limitations

The study has the usual temporal limitations associated with cross-sectional studies i.e. it is unable to predict the exposure, disease onset and outcome time relationships because both have been collected at the same time. Establishing a diagnosis of diabetes mellitus following a single fasting blood glucose has been reported to be satisfactory for an epidemiological study, such as this one. However, such a protocol could have erroneously diagnosed a proportion of pre-diabetic individuals as newly diagnosed diabetics since a second confirmatory test was not conducted. Data on the type and dose of statin therapy, as well as the reason for statin prescription were not available and therefore could not be taken into consideration during data analysis and interpretation. Oral glucose tolerance testing was not conducted as part of the population health examination survey and therefore impaired glucose tolerance (IGT) status could not considered as part of the pre-diabetes status in this study. Furthermore, since this data is self-reported, human error in drug medication reporting as well as regarding drug compliance to medication could have been in place. A small sample population in certain sub-groups could have had an effect on the power of the statistical comparisons and analysis and led to type 1 errors.

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Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interest.

References

1. Chehade JM, Gladysz M, Mooradian AD. Dyslipidemia in type 2 diabetes: prevalence, pathophysiology, and management. Drugs. 2013;73:327–39.
2. Samatha P, Venkateswarlu MSPV. Lipid profile levels in type 2 diabetes mellitus from the tribal population of Adilabad in Andhra Pradesh, India. J Clin diagnostic Res. 2012;6:590–2.
3. Reiner Ž, Tedeschi-Reiner E. Prevalence and types of persistent dyslipidemia in patients treated with statins. Croat Med J. 2013;54:339–45.
4. Inzucchi SE, Amatruda JM. Lipid management in patients with diabetes: translating guidelines into action. Diabetes Care. 2003;26:1309–11.
5. Solano MP, Goldberg RB. Lipid Management in Type 2 Diabetes. Clin Diabetes. 2006;24:27–32.
6. Ali F, Jamil H, Anwar SS, Wajid N. Characterization of lipid parameters in diabetic and non-diabetic atherosclerotic patients. J Geriatr Cardiol. 2015;12:37–43.
7. Barrett-Connor E, Grundy SM, Holdbrook MJ. Plasma lipids and diabetes mellitus in an adult community. Am J Epidemiol. 1982;115:657–63.
8. Betteridge DJ. Diabetic dyslipidaemia. Eur J Clin Investig. 1999;29(Suppl 2):12–6.
9. Daniel MJ. Lipid management in patients with type 2 diabetes. Am Heal drug benefits. 2011;4:312–22.
10. Cannon CP, Steinberg BA, Murphy SA, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. Rev Port Cardiol. 2006;25:865–8.
11. Cholesterol Treatment Trialists' (CTT), Collaborators, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581–90.
12. Wierzbicki AS, Poston R, Ferro A. The lipid and non-lipid effects of statins. Pharmacol Ther. 2003;99:95–112.
13. Chogtu B, Magazine R, Bairy KL. Statin use and risk of diabetes mellitus. World J Diabetes. 2015;6:352–7.
14. Bonetti PO, Lerman LO, Napoli C, Lerman A. Statin effects beyond lipid lowering–are they clinically relevant? Eur Heart J. 2003;24:225–48.
15. Cuschieri S, Vassallo J, Calleja N, Camilleri R, Borg A, Bonnici G, et al. Prevalence of obesity in Malta. Obes Sci Pract. 2016;2:466–70.
16. Cuschieri S, Vassallo J, Calleja N, et al. The diabesity health economic crisis-the size of the crisis in a European island state following a cross-sectional study. Arch Public Heal. 2016;74. https://doi.org/10.1186/s13690-016-0164-6.
17. Cuschieri S, Malta MJ. Mediterranean diabetes hub – A journey through the years. Malta Med J. 26.
18. Cuschieri S, Vassallo J, Calleja N, et al. The Effects of Socioeconomic Determinants on Hypertension in a Cardiometabolic At-Risk European Country. Int J Hypertens. 2017. https://doi.org/10.1155/2017/7107385.
19. Cuschieri S, Vassallo J, Calleja N, Pace NMJ. Diabetes, pre-diabetes and their risk factors in Malta: a study profile of national cross-section prevalence study. *Glob Heal Epidemiol Genomics*. 2016;1. https://doi.org/10.1017/gheg.2016.18.
20. Hockley T, Gemmill M. European Cholesterol Guidelines Report https://policy-centre.com/wp-content/uploads/2017/04/European-Cholesterol-Guidelines07.pdf (accessed 5 November 2017).
21. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome-a new world-wide definition. A consensus statement from the international diabetes federation. Diabet Med. 2006;23:469–80.
22. American Diabetes Association. Classification and Diagnosis of Diabetes. Diabetes Care 2016; 39 Suppl 1: S13–S22.
23. WHO. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. World Heal Organ. 2013:102.
24. (UK) NCGC. Statins for the primary and secondary prevention of CVD https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0071769/ (2014, accessed 6 November 2017).
25. Eldor R, Raz I. American Diabetes Association indications for statins in diabetes: is there evidence? Diabetes Care. 2009;32(Suppl 2):S384–91.
26. Goldberg IJ. Diabetic dyslipidemia: causes and consequences. J Clin Endocrinol Metab. 2001;86:965–71.
27. Taskinen M-R, Borén J. New insights into the pathophysiology of dyslipidemia in type 2 diabetes. Atherosclerosis. 2015;239:483–95.

28. Haffner SM, Mykkänen L, Festa A, et al. Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. Circulation. 2000;101:975–80.
29. Avramoglu RK, Basciano H, Adeli K. Lipid and lipoprotein dysregulation in insulin resistant states. Clin Chim Acta. 2006;368:1–19.
30. Buse K, Tanaka SHS. Healthy people and healthy profits? Elaborating a conceptual framework for governing the commercial determinants of non-communicable diseases and identifying options for reducing risk exposure. Glob Heal. 2017;13. https://doi.org/10.1186/s12992-017-0255-3.
31. Daboul MW. A study measuring the effect of high serum triglyceride and cholesterol on glucose elevation in human serum. Oman Med J. 2011;26:109–13.
32. Sattar N. Revisiting the links between glycaemia, diabetes and cardiovascular disease. Diabetologia. 2013;56:686–95.
33. Granger BB, Bosworth HB. Medication adherence: emerging use of technology. Curr Opin Cardiol. 2011;26:279–87.
34. Vanelli M, Pedan A, Liu N, Hoar J, Messier D, Kiarsis K. The role of patient inexperience in medication discontinuation: a retrospective analysis of medication nonpersistence in seven chronic illnesses. Clin Ther. 2009;31:2628–52.
35. Zullig L, Gellad W, Moaddeb J, et al. Improving diabetes medication adherence: successful, scalable interventions. Patient Prefer Adherence. 2015;9:139.
36. American Diabetes Association AD. 4. Lifestyle Management. Diabetes Care. 2017;40:S33–43.
37. Thunander Sundbom L, Bingefors K. Women and men report different behaviours in, and reasons for medication non-adherence: a nationwide Swedish survey. Pharm Pract (Granada). 2012;10:207–21.
38. Chen S-L, Lee W-L, Liang T, Liao IC. Factors associated with gender differences in medication adherence: a longitudinal study. J Adv Nurs. 2014;70:2031–40.