HYPERLIPIDEMIAS SUBTYPES ASSOCIATION WITH DIFFERENT GLYCEMIC LEVELS

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ABSTRACT

Objective: To compare lipid profile and glycemic profile in diabetic, pre-diabetic and biochemical healthy individuals.

Material and Methods: This cross-sectional study at Department of Chemical Pathology & Endocrinology, Armed Forces Institute of Pathology, Rawalpindi from July 2018 to March 2019. Samples of fasting lipid profile, fasting plasma glucose and HbA_{1c} were collected by simple random technique. At 3000 RPM for 5 minutes, these samples were then centrifuged. Using the enzymatic colorimetric methods fasting plasma glucose, total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) and very low density lipoprotein cholesterol (VLDL-C) were analyzed on ADVIA1800 and glycosylated hemoglobin (HbA_{1c}) analysis was facilitated by turbidometry inhibition immunoassay (TINIA) using ADVIA1800. For the statistical analysis SPSS 22 was used.

Results: Out of 141 selected subjects 72 (51.1%) were males and 69 (48.9%) were females. On the basis of fasting plasma glucose and HbA1c values, outcome variable was divided into following three categories; healthy group 18 (12.8%), pre-diabetic 40 (28.4%) and diabetic 83 (58.9%). Mean age in healthy, prediabetic and diabetic groups were 45.9±18.3 years, 52.3±11.1 years, 55.4±10.2 years respectively. The results deducted from the lipid profile analysis suggest; out of these 141 patients 21 (14.9%) were healthy, 15(10.6%) with familial combined hyperlipidemias (FCH), 12(8.5%) had familial cholesterolemia (FH), 2(1.4%) were with hypertriglyceridemia, and 91(64.6%) were of nonspecific dyslipidemias. Different hyperlipidemia (according to Frederickson 's classification) and nonspecific dyslipidemia percentage distribution in three glycemic profile categories was; diabetic group included normal lipid profile = 9 (10.8%), FH = 8 (9.6%), FCH = 7 (8.4%), hypertriglyceridemia = 2 (2.4%) and nonspecific dyslipidemia = 57 (68.7%), pre-diabetic group included normal lipid profile =7 (17.5%), FH = 7 (17.5%), FCH = 5 (12.5%) and nonspecific dyslipidemia = 21 (52.5%) and healthy group included lipid profile within reference range= 5 (27.8%) and nonspecific dyslipidemias = 13(72.2%). The non- specific dyslipidemias groups had been further divided into different groups; 1st group included only decrease HDL-C= 21(23%), 2nd group included increase VLDL-C and decrease HDL-C = 15 (17%), 3rd group included decrease HDL-C increase LDL-C and increase total cholesterol (TC) of 38 (42%) and 4th group included decrease HDL-C, increase Triglyceride (TG), increase VLDL-C with decrease HDL-C 16(18%).

Conclusion: Nonspecific dyslipidemia was found with highest frequency in healthy than pre-diabetic and diabetic population.

Key Words: Nonspecific dyslipidemias, HDL-C, LDL-C, VLDL-C.

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INTRODUCTION

In younger population, diabetes and hyperlipidemia are said to be two paramount cardio-metabolic risks leading to the development of premature heart disease. The identifying features of type 2 diabetes mellitus include persistent hyperglycemia accompanied with inadequacy of insulin levels [1]. The characterization of diabetic dyslipidemia includes elevated post-parandinal, fasting triglycerides and LDL-cholesterols levels, minute levels of HDL-cholesterol and with high presence of small dense LDL-C particles [2]. The changes in these lipid concentrations denote the connection between diabetes and premature heart disorders. Insulin resistance can occur in pancreas, skeletal muscles and hepatic tissue along with changes in different cholesterol pathways. This is mainly caused by chronic inflammation and its mediators; TNF-alpha and IL-6, which alter the concentration of different lipoprotein cholesterol in blood [3]. A comparison between vascular complications of diabetes and hyperlipidemia has been a topic of interest as they are likely to occur

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mainly in type 2 diabetes rather than prediabetic and healthy population [4].

Glycemic levels divide the general population into three categories; healthy, prediabetic (either impaired fasting glucose or impaired glucose tolerance) and diabetic. According to American Diabetic Association 2004, Impaired fasting glucose (IFG) was defined as fasting plasma glucose (FPG) occurs between ≥5.6 & ≤ 7.0 mmol/L, and Diabetes when FPG ≥7.0 mmol/L or history of diabetes or patients on glycemic medications regardless of the FPG values and healthy with FPG < 5.6 mmol/l [5]. The dyslipidemia is categorized into primary and secondary type [6]. Fredrickson classified the primary cause initially into four categories; Familial lipoprotein lipase deficiency with increased triglycerides and decreased HDL-C (type I). Familial Hypercholesterolemia (FH) with increased total cholesterol and LDL-cholesterol (Fredrickson type IIa). Familial Combined Hyperlipidemia (FCH) with increased total cholesterol, LDL-cholesterol and triglycerides (type IIb), Familial Dysbetalipoproteinaemia with increased total cholesterol and triglycerides (type III) and Familial Hypertriglyceridemia with increased triglycerides (type IV) [7]. The most common secondary causes are diabetes and chronic kidney disorders This secondary type of dyslipidemia was called nonspecific dyslipidemia [8]. Previous studies show a link between insulin resistance, which is a precursor to type 2 diabetes, and diabetic dyslipidemia, atherosclerosis and premature coronary blood vessel disease [9, 10, 11]. However, these conditions can occur even before the diagnosis of diabetes so in order to find the difference of lipid profile at different glycemic levels, we planned a study with the objective to compare the lipid profile and glycemic profile parameters in diabetics, prediabetics, and healthy population of Pakistan.

MATERIAL AND METHODS

This study was conducted at Department of Chemical Pathology & Endocrinology, Armed Forces Institute of Pathology, Rawalpindi from July 2018 to March 2019 after taking ethical permission. The sample size calculator from WHO was used. 141 individuals were selected by simple random technique. Adults ranging from 18-80years of either gender were included in the study. The study excluded individuals such as pregnant women, indoor, on anti-cholesterol treatment and those having acute & chronic illness. Samples were taken from individuals visiting the AFIP reception after taking their consent in fasting condition for lipid profile and diabetic profile. Gel tubes were used for fasting lipid profiles, sodium fluoride tubes for glucose and k-EDTA tube for HbA_{1c}. Within half an hour, specimens were labelled and transferred to the processing room. To separate the serum, samples were centrifuged at 3000 RPM for 3 minutes. Within 2 hours of sample collection, analysis was performed. Using the enzymatic colorimetric methods fasting plasma glucose, total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) and very low density lipoprotein cholesterol (VLDL-C) were analyzed on ADVIA1800 and glycosylated Hemoglobin (HbA_{1c}) analysis was facilitated by Turbidometry Inhibition Immunoassay (TINIA) using ADVIA1800. LDL-C was also calculated by Friedewald's formula when triglycerides were < 4.5 mmol/l. Data was entered on Statistical Package for the Social Sciences (SPSS) version 22. The calculations of descriptive statistics mean and SD and frequency and percentage for qualitative data were made. One-way ANOVA was used as interferential statistics between three groups (healthy, prediabetics and diabetics) comparison against all quantitative variables considering p-value <0.05 as statistically significant.

RESULTS

Out of 141 selected subjects 72 (51.1%) were males and 69 (48.9%) were females. On the basis of fasting plasma glucose and HbA_{1c} values, outcome variable was divided into following three categories; Healthy group 18 (12.8%), pre-diabetic 40 (28.4%) and diabetic 83 (58.9%). Mean age in healthy, prediabetic and diabetic group were 45.9±18.3 years, 52.3±11.1 years, and 55.4±10.2 years respectively. The results deduced from the lipid profile analysis showed that out of these 141 patients, 21 (14.9%) were healthy, 15(10.6%) had familial combined hyperlipidemias (FCH), 12(8.5%) had familial cholesterolemia (FH), 2(1.4%) were with hypertriglyceridemia, and 91(64.6%) were of nonspecific dyslipidemias as shown in figure 1. Different hyperlipidemia (according to Frederickson 's classification) and nonspecific dyslipidemia percentage distribution in three glycemic profile categories was; diabetic group included normal lipid profile = 9 (10.8%), FH = 8 (9.6%), FCH = 7 (8.4%), hypertriglyceridemia = 2 (2.4%) and nonspecific dyslipidemia = 57 (68.7%), pre-diabetic group included normal lipid profile =7 (17.5%), FH = 7 (17.5%), FCH = 5 (12.5%) and nonspecific dyslipidemia = 21 (52.5%) and healthy group included lipid profile within reference range= 5 (27.8%) and nons-pecific dyslipidemias = 13(72.2%).

The non- specific dyslipidemias groups had been further divided into different groups; 1st group included only decrease HDL-C= 21(23%), 2nd group included increase VLDL-C and decrease HDL-C = 15 (17%), 3rd group included decrease HDL-C increase LDL-C and increase total cholesterol (TC) of 38 (42%) and 4th group included decrease HDL-C, increase Triglyceride (TG), increase VLDL-C with decrease HDL-C 16(18%). Descriptive statistics (Mean ± SD) of study population was compared in three groups (healthy, prediabetic and diabetic) for all quantitative variables likes; age (years), fasting plasma glucose (mmol/l), HbA_{1c}(%), Total cholesterol (mmol/l), HDL-C (mmol/l), LDL-C(mmol/l), TG(mmol/l), VLDL-C (mmol/l), LDL-C (mmol/l) with 95% confidence interval for mean, their maximum and minimum values and total no of participants in these three groups was shown in the table-1 while One way ANOVA with Post Hoc Tests showed that there were significant difference among all three groups in HbA_{1c} (p-value -0.000) and FPG (p-value-0.000), TG (p-value -0.000) between (prediabetic and diabetic) and (healthy and diabetic) while healthy group also showed significant difference in age (p-value-0.006) from diabetic group while non-significant difference observed against all others quantitative variables between these three groups as shown in table-2.

Table-1: Baseline Characteristics of study population

Study Parameters		No of participants	Mean± SD	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Limit	Upper Limit		
Age (Years)	Healthy	18	45.9±18.3	36.83	55.05	15.00	75.00
	Prediabetes	40	52.3±11.2	48.76	55.88	34.00	74.00
	Diabetes	83	55.4±10.2	53.21	57.69	16.00	80.00
	Total	141	53.3±12.1	51.33	55.37	15.00	80.00
Fasting Plasma Glucose (mmol/l)	Healthy	18	5.1±0.56	4.83	5.39	4.10	6.40
	Prediabetes	40	5.40.86	5.17	5.73	3.90	8.20
	Diabetes	83	7.7±2.7	7.16	8.38	3.90	18.90
	Total	141	6.7±2.5	6.36	7.19	3.90	18.90
HbA_{1c} (%)	Healthy	18	4.7±0.47	4.54	5.01	4.10	5.60
	Prediabetes	40	6.0±0.33	5.94	6.15	5.10	6.70
	Diabetes	83	7.9±1.18	7.70	8.22	6.10	11.30
	Total	141	7.0±1.5	6.76	7.26	4.10	11.30
Total cholesterol (mmol/l)	Healthy	18	4.4±0.99	3.91	4.90	3.20	7.45
	Prediabetes	40	4.70±1.09	4.35	5.05	2.28	7.48
	Diabetes	83	4.60±1.22	4.33	4.86	.90	7.69
	Total	141	4.60±1.16	4.41	4.79	.90	7.69
HDL-C (mmol/l)	Healthy	18	1.17±0.63	.86	1.49	.03	3.00
	Prediabetes	40	1.16±0.34	1.05	1.27	.68	2.30
	Diabetes	83	1.04±0.30	.98	1.11	.40	2.27
	Total	141	1.09±0.37	1.03	1.16	.03	3.00
Non-HDL-C (mmol/l)	Healthy	18	3.22±0.93	2.76	3.68	2.17	6.35
	Prediabetes	40	3.54±1.05	3.21	3.88	1.18	5.91
	Diabetes	83	3.58±1.09	3.34	3.82	1.37	6.20
	Total	141	3.52±1.06	3.35	3.70	1.18	6.35
LDL-C (mmol/l)	Healthy	18	2.62±0.90	2.17	3.07	1.36	5.02
	Prediabetes	40	2.78±1.00	2.45	3.10	.33	4.58
	Diabetes	83	2.59±1.03	2.36	2.81	.56	4.78
	Total	141	2.65±1.00	2.48	2.81	.33	5.02
VLDL-C (mmol/l)	Healthy	18	0.63±0.36	.45	.82	.28	1.39
	Prediabetes	40	0.72±0.43	.58	.87	.22	2.66
	Diabetes	83	0.94±0.58	.81	1.07	.20	4.40
	Total	141	0.84±0.53	.75	.93	.20	4.40
Triglyceride (mmol/l)	Healthy	18	1.29±0.80	.89	1.69	.49	3.04
	Prediabetes	40	1.55±1.00	1.23	1.88	.55	5.86
	Diabetes	83	2.34±1.40	2.03	2.65	.52	6.17
	Total	141	1.98±1.30	1.77	2.20	.49	6.17

Table-2: Post Hoc tests for multiple comparison of study population.

Dependent Variable	Groups	Outcomes	Sig. p-value	95% Confidence Interval	
				Lower Limit	Upper Limit
Age	Healthy	Prediabetes	.140	-14.3017	1.5406
		Diabetes	.006	-16.7699	-2.2569
	Prediabetes	Healthy	.140	-1.5406	14.3017
		Diabetes	.353	-8.5047	2.2390
	Diabetes	Healthy	.006	2.2569	16.7699
		Prediabetes	.353	-2.2390	8.5047
Fasting Plasma Glucose	Healthy	Prediabetes	.852	-1.8266	1.1500
		Diabetes	.000	-4.0214	-1.2946
	Prediabetes	Healthy	.852	-1.1500	1.8266
		Diabetes	.000	-3.3290	-1.3104
	Diabetes	Healthy	.000	1.2946	4.0214
		Prediabetes	.000	1.3104	3.3290
HbA1c%	Healthy	Prediabetes	.000	-1.9063	-.6381
		Diabetes	.000	-3.7675	-2.6056
	Prediabetes	Healthy	.000	.6381	1.9063
		Diabetes	.000	-2.3444	-1.4843
	Diabetes	Healthy	.000	2.6056	3.7675
		Prediabetes	.000	1.4843	2.3444
Total cholesterol	Healthy	Prediabetes	.638	-1.0829	.4845
		Diabetes	.800	-.9108	.5251
	Prediabetes	Healthy	.638	-.4845	1.0829
		Diabetes	.884	-.4251	.6379
	Diabetes	Healthy	.800	-.5251	.9108
		Prediabetes	.884	-.6379	.4251
HDL-C	Healthy	Prediabetes	.989	-.2346	.2650
		Diabetes	.365	-.0976	.3601
	Prediabetes	Healthy	.989	-.2650	.2346
		Diabetes	.239	-.0534	.2854
	Diabetes	Healthy	.365	-.3601	.0976
		Prediabetes	.239	-.2854	.0534
Non-HDL-C	Healthy	Prediabetes	.537	-1.0403	.3950
		Diabetes	.404	-1.0150	.2999
	Prediabetes	Healthy	.537	-.3950	1.0403
		Diabetes	.984	-.5216	.4518
	Diabetes	Healthy	.404	-.2999	1.0150
		Prediabetes	.984	-.4518	.5216
LDL-C	Healthy	Prediabetes	.846	-.8364	.5209
		Diabetes	.993	-.5927	.6508
	Prediabetes	Healthy	.846	-.5209	.8364
		Diabetes	.602	-.2735	.6470
	Diabetes	Healthy	.993	-.6508	.5927
		Prediabetes	.602	-.6470	.2735
VLDL-C	Healthy	Prediabetes	.808	-.4439	.2591
		Diabetes	.065	-.6290	.0150
	Prediabetes	Healthy	.808	-.2591	.4439
		Diabetes	.087	-.4530	.0238
	Diabetes	Healthy	.065	-.0150	.6290
		Prediabetes	.087	-.0238	.4530
Triglyceride	Healthy	Prediabetes	.736	-1.0966	.5709
		Diabetes	.004	-1.8131	-.2856
	Prediabetes	Healthy	.736	-.5709	1.0966
		Diabetes	.004	-1.3519	-.2211
	Diabetes	Healthy	.004	.2856	1.8131
		Prediabetes	.004	.2211	1.3519

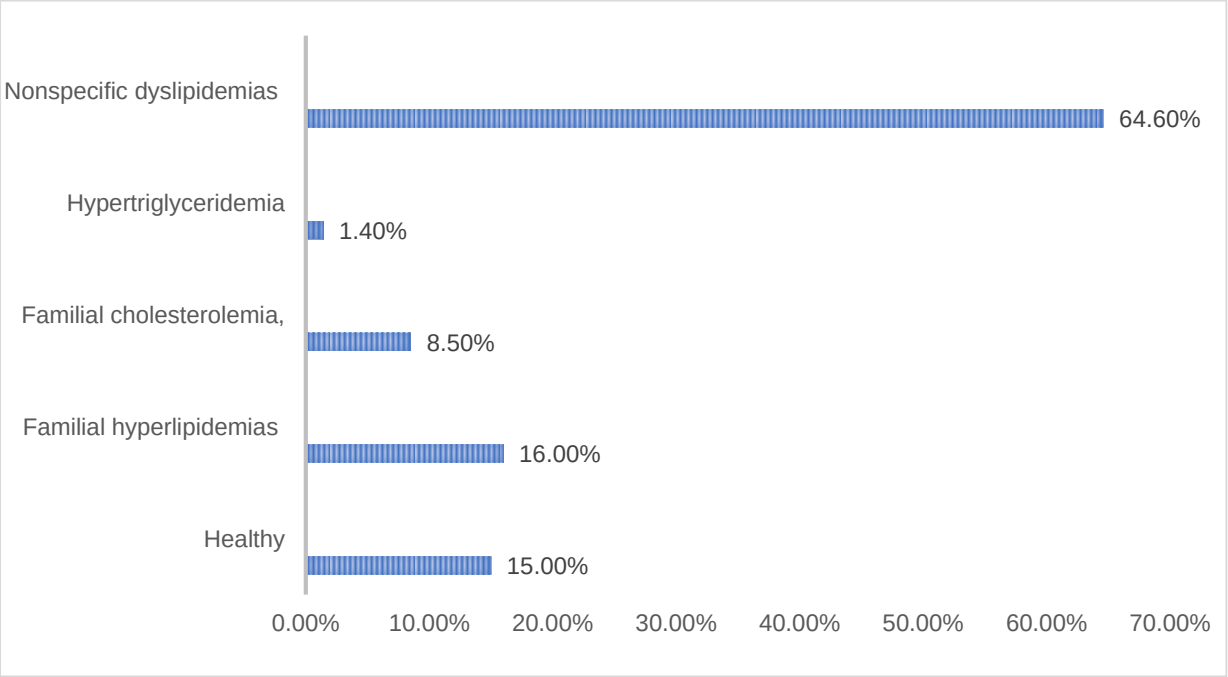

Figure-1: Distribution of different types of hyperlipidemias in study population.

DISCUSSION

Our study had following results; Majority of our population was male and with increasing age, their diabetic status was changed showing that the age itself had greater influenced on insulin resistance and development of type 2 diabetes mellitus. It showed that most frequently occurring lipid disorder was nonspecific dyslipidemias which was most primarily present 72.2% in healthy participants than in diabetic (68.7%) and prediabetic (52.5%). Among this non- specific dyslipidemia, the group with highest frequency i.e. 42% had decreased HDL-C, increased LDL-C and increased total cholesterol (TC) derangements. In literature it was reported that this nonspecific dyslipidemia could be initiated in healthy population with and without insulin resistance and could also be converted into other secondary type of dyslipidemia like diabetic dyslipidemia that was characterized by low HDL-cholesterol, elevated LDL cholesterol and instead of elevated cholesterol into elevated fasting & postprandial (random) triglycerides and the predominance of small dense LDL particles. Its presence in healthy population was alarming and predictive of underlining insulin resistance [3,10].

It could be speculated that if we could control this nonspecific dyslipidemia progression in healthy population, we may be able to manage insulin resistance and progression of diabetic (micro vascular and macro vascular) complications. This fact was also studied previously which showed that HbA_{1C} even within non-diabetic level is a predictor of cardiovascular disease in a general Japanese population. Joint Committee for Comprehensive Risk Management Chart for the prevention of cerebro-cardiovascular diseases also emphasized the importance of high HbA_{1c} levels with the increased risk of developing cardiovascular disease [3,12,13].

Our study also highlighted that HbA_{1c} was significantly different in healthy, prediabetic and diabetic population as having an elevated trend, however, its levels were high (toward upper reference limit) in healthy population. Authors had also quoted in literature that Type-2 diabetes mellitus causes cardiovascular disease through diabetic dyslipidemia which was a type of nonspecific dyslipidemia and with management of this dyslipidemia, the risk for cardiovascular events could be reduced. Type 2 diabetes mellitus incidence was doubled between 1980 and 2012 in the USA and it increased to approximately 1.4 million in 2014 [11]. Cardiovascular disease (CVD) is the leading cause of death around the world particularly in patients with diabetes mellitus [14]. In a cohort study, smaller reductions in adverse cardiovascular outcomes were observed among diabetics than non-diabetics [15]. Total cholesterol and LDL-C- were low in healthy population, touching their peak in pre diabetic and then decreased in diabetes mellitus patients, it may be due to exhaustion of their receptors. Literature also documented cardiovascular events in patients having total cholesterol and LDL-C within reference

limit and emphasized research to find new biomarkers for this disease [16, 17].

Our study showed that triglycerides were very high in diabetic group and had significant difference between this group with prediabetic and healthy group while the differences were not significant between healthy and prediabetic. VLDL-C and non-HDL-C were elevated and had tendency for poor glycemic control and low HDL-C. These facts were similar to previous documented studies done in Japanese northern rural population [18,19,20,21]. Literature also documented the emerging importance of non HDL-C as a predictor of premature cardiovascular diseases in younger population who had total cholesterol and LDL-C within reference limit and their analysis was done by enzymatic method for total cholesterol and triglyceride and homogenous method for LDL-C and HDL-C similar to our study [22,23,24]. Limitation of our study was that it was a hospital based, single centered study, usually having the influx of more ill patients than healthy and asymptomatic individuals, hence exhibiting diabetics with higher frequency.

CONCLUSION

Nonspecific dyslipidemia was most frequent in healthy than pre-diabetic and diabetic population; this finding signifies that nonspecific dyslipidemia represent the major link towards cardiovascular diabetic complications with different levels of glycaemia.

AUTHORS CONTRIBUTION

Safia Fatima: Planning, data collection, analysis and manuscript writing.

Haseeba Nigarish Shabbir: Data collection.

Muhammad Aamir, Afshan Bibi, Sobia Irum Kirmani, & Muhammad Tahir Khadim: Revised manuscript.

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