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Research paper

Low HDL-cholesterol among normal weight, normoglycemic offspring of individuals with type 2 diabetes mellitus

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ABSTRACT

OBJECTIVE: Offspring of type 2 diabetics have an increased risk of dyslipidemia, glucose intolerance and obesity. The aim of this study was to assess the lipid levels in the offspring of diabetics with normal glucose tolerance and normal body weight. DESIGN: Normal weight offspring of patients with type 2 diabetes mellitus (DM) who had normal glucose tolerance, and healthy gender matched controls of comparable age without a family history of diabetes mellitus, were the subjects of this study. Lipid profiles were determined in cases and controls. RESULTS: The study included 114 subjects (64 males and 50 females) in each group, aged (mean±SD) 24.0±7.9 in cases and 24.1±8.0 years in controls. The body mass index (BMI) was 20.8±3.0 and 20.2±3.1 kg/m^2 in cases and controls, respectively. Serum total cholesterol, triglycerides, plasma glucose, fasting insulin, C-peptide and proinsulin levels were comparable in cases and controls. Serum high density lipoprotein (HDL) cholesterol was lower ($p < 0.001$), whilst the serum triglyceride/HDL ratio, low density lipoprotein (LDL) cholesterol and area under the curve for insulin and proinsulin during an oral glucose tolerance test were higher in cases compared to controls. HDL cholesterol showed no significant correlation with plasma glucose, insulin or proinsulin. CONCLUSION: Plasma HDL cholesterol is low among normal weight, normoglycemic offspring of subjects with type 2 diabetes mellitus. The implications of this finding are not apparent.

Key words: Beta cell function, Cardiovascular risk factor, Glucose intolerance, HDL-cholesterol, Insulin sensitivity, Offspring of diabetics, Proinsulin

INTRODUCTION

Cardiovascular disease (CVD) is among the most common causes of morbidity and mortality worldwide.[1] The risk factors for CVD include sedentary lifestyle, unhealthy eating habits, cigarette smoking, hypertension, dyslipidemia and diabetes mellitus (DM).[2] Dyslipidemia constitutes a significant risk factor for CVD and an integral part of both DM and CVD.[3] However, the exact lipid species that is responsible for this is not clear.

Insulin resistance and type 2 DM are generally

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accompanied by low levels of high density lipoprotein (HDL) cholesterol and high plasma triglycerides.[4-9] Similar findings have also been found in the offspring of individuals with type 2 DM, this mainly attributed to the increased risk of obesity, hyperinsulinemia and glucose intolerance.[7,10-12] However, it is not yet clear whether a family history of DM per se is associated with dyslipidemia, or dyslipidemia is related to the obesity, hyperinsulinemia or glucose intolerance, usually present in subjects with family history of type 2 DM. The aim of this study was to assess lipid levels among normal weight, normoglycemic offspring of individuals with type 2 DM. Only normal weight subjects [body mass index (BMI) <25kg/m^2] with normal glucose tolerance were included to avoid the confounding effect of obesity and glucose intolerance.

SUBJECTS AND METHODS

Subjects

Normal weight subjects (BMI <25kg/m^2 for adults and BMI values indicative of obesity, according to International Obesity Task Force (IOTF) criteria, for those ≤18 years)[13] with normal glucose tolerance, aged 5 to 55 years, and a parent or grandparent with type 2 DM were included in the study. Normal weight, gender matched controls of comparable age with normal glucose tolerance and no family history of DM formed the control group. The controls were recruited from the community. The study details were explained during group discussions with students and residents of various areas and gender matched controls of comparable age were enrolled from those who volunteered to participate.

The study protocol was approved by the institutional Ethics Committee. Written informed consent was obtained from all participants prior to enrollment. In the case of children (less than 18 years), consent was obtained from one of the parents and verbal assent was taken from the child (7 years or more), as per Indian Council of Medical Research (ICMR) guidelines.

Inclusion criteria

Cases: Subjects with parents or grandparents with type 2 DM, aged 5 to 55 years, with normal glucose tolerance and normal weight.

Controls: Same as for cases except for negative history of DM in parents, siblings or grandparents.

Exclusion criteria: Obesity, glucose intolerance, age more than 55 or less than 5 years, pregnancy, lactation, presence of any chronic illness or medication.

Sample size calculation: A pilot study of 15 cases with the same inclusion and exclusion criteria and 15 gender matched controls of comparable (±1 year) age was conducted for sample size calculation. The information on HDL-cholesterol was used for the calculation sample size. The mean±SD of HDL-cholesterol in cases was 1.1±0.29 (mmol/l) and in controls 1.23±0.4 (mmol/l). For a power of 80% and a p value of 0.05, 114 subjects were needed in each group.

A detailed family tree was drawn with special reference to history of type 2 DM. Details of medical history were collected and physical examination including anthropometry was performed. Height was measured with a stadiometer to the nearest centimeter and weight was registered to the nearest kg. BMI was calculated as the weight (kg) divided by the square of the height in meters. A BMI value of 25 or more was considered as overweight for the adult population. For children and adolescents up to 18 years cut-offs recommended by the IOTF were used.[13] Waist circumference was measured midway between the lowest rib and the superior border of the iliac crest with an inelastic measuring tape. The hip circumference was measured at the greatest posterior protuberance of buttocks with the subject standing erect, feet together. Both measurements were done to the nearest centimeter. For the oral glucose tolerance test, subjects were advised to follow a normal diet and abstain from alcohol for three days prior to the test. After 10-12 hours of overnight fast, the 75gm (1.75g/kg body weight for children) oral glucose tolerance test (OGTT) was performed. Blood samples were collected at 0, 30, 60 and 120 min after oral glucose for the determination of glucose, insulin, C-peptide and proinsulin. A fasting blood sample was used for haematological indices, renal and liver function tests and lipid profile.

Two hundred and eleven subjects with family history of DM volunteered for the study and underwent the glucose tolerance test. From these, 114 subjects

with normal glucose tolerance were selected as cases and 114 gender matched controls of comparable age, with normal glucose tolerance and without family history of DM, were enrolled as controls. Cases were recruited first and gender matched controls of comparable age (±1 years) were enrolled for each case.

Analytical measurements

Plasma glucose was assayed by the glucose oxidase method on a Labmate 20 Analyser (Trivitron Diagnostics, Chennai, India). Serum triglycerides and total cholesterol were measured by enzymatic methods. HDL-cholesterol was measured after precipitation of chylomicrons, and very low density lipoprotein (VLDL) and low density lipoprotein (LDL) fractions by phosphotungstic acid and magnesium chloride. HDL-cholesterol remained in the supernatant after centrifugation and was measured by the enzymatic cholesterol method. LDL cholesterol was calculated from data of the above parameters by Friedewald's equation. Intra-assay coefficient of variation (CV) for total cholesterol, triglyceride and HDL-cholesterol were 1.9%, 1.9% and 4.5%, respectively, whereas inter-assays CV were 2.5%, 2.7% and 4.9%, respectively.

Plasma insulin was measured by electro-chemiluminescence assay employing ELECSYS 2010 (Roche Diagnostics, Indianapolis, USA). This assay uses monoclonal antibodies against insulin and has 0.05% cross-reactivity with human proinsulin and its split forms. Intra-assay CV was 5.1% and inter-assay CV was 5.7%. C-peptide is also measured by electro-chemiluminescence assay. For C-peptide intra-assay CV was 3.9% and inter-assay CV was 3.9%. Serum proinsulin was measured by a radioimmunoassay kit (Catalog No. HPI-15K, Millipore Corporation, Billerica, MA). This assay cross-reacts neither with human insulin (<0.1%)[14] nor with C-peptide (0.1%). It has 100% specificity for intact human proinsulin and 95% with des 31,32 human proinsulin.[14] Intra- and inter-assay CV of proinsulin were 5.9% and 6.9%, respectively. Percentage of body fat was measured by the dual energy X-ray absorptiometry (DXA) method using a HOLOGIC QDR 4500W densitometer (Hologic Inc, Bedford, MA).

Glucose tolerance was classified as per the American Diabetes Association (ADA) 2003 criteria.[15] Abnormalities of lipids were defined as per the National Cholesterol Education Program (NCEP) III criteria (Adult Treatment Panel III Final Report) for subjects above 18 years.[16] For children and adolescents up to 18 years, dyslipidemia was defined as per American Heart Association guidelines for Primary Prevention of Atherosclerotic Cardiovascular Disease beginning in Childhood.[17] Area under the curve (AUC) was calculated by the formula according to Tai's method.[18] Insulin resistance index, homeostasis model assessment-insulin resistance (HOMA-IR) was calculated as described by Matthews et al,[19] and whole body insulin sensitivity index (WBISI) as described by Matsuda et al.[20] Disposition Index was calculated as the product of area under the curve of C-peptide/ area under the curve of glucose and whole body insulin sensitivity index, making a variation from the formula described by Retnakaran et al, where insulin was used in the place of C-peptide.[21]

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 15 software. The data were expressed as mean ± SD. Log transformation was also applied to skewed data for insulin, triglyceride (TG), TG to HDL ratio, HOMA-IR, whole body insulin sensitivity index, disposition index and for area under the curves of insulin, C-peptide and proinsulin, while the Student 't' test was used for comparison of the two groups. A chi square test was done to evaluate the difference in frequency between the two groups. Pearson correlation was applied to find the relationship between continuous-numeric parameters. A forward stepwise multiple linear regression was performed to determine the effect of possible predictors on serum HDL and LDL cholesterol levels. P value <0.05 was considered as significant.

RESULTS

One hundred and fourteen cases and controls completed the study. There were 64 males and 50 females in each group. Age ranged from 5 to 53, mean ± SD of 24±7.9 in cases and 24.1±8.0 years in controls (Table 1). Age, BMI, waist to hip ratio, blood glucose levels, C-peptide levels, HOMA-IR, insulin sensitivity, as measured by whole body insulin sensitivity index and disposition index measured

from glucose and C-peptide data during OGTT, were comparable between the two groups. Insulin at 60 minutes (p=0.027) after oral glucose and area under the curves of insulin (p=0.046) and proinsulin (p=0.016), as well as proinsulin at 30 minutes (p=0.025) and 60 minutes (p=0.019) after oral glucose were significantly higher in cases compared to controls. There was a significantly higher ratio of area under the curve of proinsulin to area under the curve of C-peptide in cases compared to controls, indicating a relative

Table 1. Lipids and glucose homeostasis parameters in cases and controls

Parameter	Cases (mean ± SD) n:114	Controls (mean ± SD) n:114	P value
Age (years)	24.0±7.9	24.1±8.0	0.875
BMI (kg/m^2)	20.8±3.0	20.2±3.1	0.154
Triglyceride (mmol/l)	1.33±0.57	1.26±0.64	0.251
Total cholesterol (mmol/l)	4.07±0.78	3.96±0.83	0.322
HDL (mmol/l)	1.09±0.22	1.21±0.27	<0.001*
LDL (mmol/l)	2.36±0.69	2.17±0.75	0.046*
TG to HDL ratio	3.0±1.7	2.6±1.7	0.013*
Glucose 0 (mmol/l)**	4.76±0.32	4.78±0.41	0.659
Glucose 30 min	6.89±1.36	6.66±1.00	0.163
Glucose 60 min	6.04±1.31	5.92±1.15	0.453
Glucose 120 min	5.07±0.93	5.23±0.92	0.209
AUC glucose (mmol/l min^{-1})	700±101	692±89	0.544
Insulin 0 (µIU/ml)**	8.5±4.7	7.7±3.7	0.118
Insulin 30 min	72.8±47	67.0±41	0.162
Insulin 60 min	59±28	51±34	0.027*
Insulin 120 min	37±31	31±19	0.139
AUC insulin (nmol/l min^{-1})	41.6±23.3	36.4±20.0	0.046*
AUC C-peptide (nmol/l min^{-1})	250±80	242±83	0.393
Proinsulin 0 (pmol/l)**	11.6±5.7	10.2±4.0	0.278
Proinsulin 30 min	32.3±14	28.3±13	0.025*
Proinsulin 60 min	39.2±17	33.9±16	0.019*
Proinsulin 120 min	39.7±17	35.4±17	0.081
AUC proinsulin (nmol/l min^{-1})	4.05±1.6	3.53±1.5	0.016*
Waist to hip ratio	0.85±0.06	0.86±0.07	0.643
Body fat %	34.5±7.1	32.6±8.0	0.318
HOMA-IR	1.8±1.0	1.66±0.8	0.135
WBISI	7.1±3.6	8.4±6.7	0.061
Disposition index	2.32±0.8	2.61±1.3	0.071
AUC proinsulin/AUC C-peptide	0.0173±0.007	0.0155±0.005	0.04*

BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides; HOMA-IR: homeostasis model assessment-insulin resistance; AUC: area under the curve, WBISI: whole body insulin sensitivity index.
*Significant at 0.05 level. **Values during an oral glucose tolerance test.

hyper-proinsulinemia in cases (p=0.04).

There was no statistically significant difference in plasma triglyceride or total cholesterol between the two groups. LDL-cholesterol was marginally higher in cases compared to controls (p=0.046). The cases had lower HDL-cholesterol (1.09±0.22 vs 1.21±0.3, p <0.001) and higher triglyceride to HDL-cholesterol ratio (3.0±1.7 vs 2.6±1.7, p=0.013). Percent body fat was not statistically different between cases and controls. Table 2 compares the number of subjects with abnormal lipid levels. The number of subjects with low HDL-cholesterol (<1.03 mmol/l for age >18 and 0.9 mmol/l for age ≤18) was higher in cases compared to controls (p=0.015). The probability (based on odds ratio) of HDL below limit was almost two times higher for cases compared to controls.

A sub-analysis of the data was carried out based on the age of the subjects (age up to 24 years and ≥24 years) (Table 3). In the younger age group (<24 years), HDL-cholesterol was significantly lower (p=0.017) and TG to HDL ratio was significantly higher (p=0.02) in cases compared to controls. AUC proinsulin/AUC C-

Table 2. Frequencies of lipid abnormalities in cases (n 114) and controls (n 114)

Lipid abnormality	Offspring of diabetics n (%)	Controls n (%)	P value *	Odds ratio 95% CI
Triglyceride ≥1.69 mmol/l	26 (22.8)	19 (16.7)	0.244	1.48 (0.73-3.01)
Total cholesterol ≥5.2 mmol/l#	13 (11.4)	16 (14.0)	0.551	0.79 (0.34-1.84)
HDL-cholesterol <1.03 mmol/l##	45 (39.4)	28 (24.5)	0.015*	2.0 (1.09-3.68)
LDL-cholesterol ≥2.58 mmol/l###	42 (36.8)	29 (25.4)	0.06	1.71 (0.93-3.1)

HDL: high density lipoprotein; LDL: low density lipoprotein;
Limit used for up to age 18 years: # ≥4.4 mmol/l, ## ≤0.9 mmol/l, ### ≥2.84 mmol/l. *Significant at 0.05 level.

Table 3. Lipid and glucose homeostasis parameters in the two sub-groups of cases and controls classified on the basis of age (age <24 years and age ≥24 years)

	Age <24 years			Age ≥24 years		
Parameter	Cases n:62	Controls n:62	P value	Cases n:52	Controls n:52	P value
Age (years)	18.5±4.3	18.7±4.5	0.76	30..5±6.0	30.6±6.4	0.95
BMI (kg/m^2)	19.7±3.1	19.2±2.9	0.38	22.2±2.2	21.5±2.8	0.16
Triglyceride (mmol/l)	1.25±0.5	1.08±0.4	0.07	1.41±0.6	1.46±0.8	0.97
Total cholesterol mmol/l	3.77±0.7	3.75±0.8	0.84	4.43±0.8	4.22±0.84	0.21
HDL (mmol/l)	1.10±0.23	1.22±0.3	0.017*	1.07±0.23	1.20±0.21	0.005*
LDL (mmol/l)	2.09±0.6	2.03±0.7	0.57	2.69±0.6	2.35±0.8	0.02*
TG to HDL ratio	2.78±1.5	2.2±1.1	0.02*	3.3±1.9	3.0±2.2	0.27
AUC glucose (mmol/l min^{-1})	685.4±92	685.7±80	0.97	717±109	701±98	0.45
AUC insulin (nmol/l min^{-1})	39.7±22	34.6±15	0.14	43.8±24	38.4±24	0.07
AUC proinsulin (nmol/l min^{-1})	4.12±1.7	3.69 ±1.4	0.17	3.96 ±1.4	3.74±1.8	0.22
AUC proinsulin/AUC C-peptide	0.019±0.008	0.016±0.005	0.02*	0.015±0.004	0.015±0.004	0.63
WBISI	7.2±3.5	7.9±3.9	0.18	6.9±3.7	9.0±8.9	0.19
Disposition index	2.24±0.6	2.53±1.1	0.09	2.42±0.9	2.70±1.5	0.36

BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides; AUC: area under the curve; WBISI: whole body insulin sensitivity index.
*Significant at 0.05 level.

peptide was also significantly higher (p=0.02) in cases. Insulin sensitivity, disposition index, serum TG, total and LDL-cholesterol were not significantly different. In the higher age (≥24 years) group, along with low HDL levels (p=0.005) there was significantly higher LDL-cholesterol in cases (p=0.02). Serum TG, total cholesterol, area under curves of glucose, insulin, proinsulin, AUC proinsulin/AUC C-peptide, whole body insulin sensitivity index and disposition index showed no significant difference between cases and controls.

In Table 4 the correlation between area under the curve of glucose, insulin and proinsulin with lipid levels is demonstrated. Area under the curve of glucose showed correlation with triglyceride levels in both cases (p=0.050) and controls (p=0.020). Area under the curve of insulin correlated with total cholesterol and LDL-cholesterol in cases (p=0.010), and with triglyceride levels in controls (p <0.001). The area under the curve of proinsulin showed correlation with triglyceride levels only in controls (p=0.003) and marginal non-significant correlation in cases (p=0.056). HDL-cholesterol did not show any statistically significant correlation with area under the curves of glucose, insulin or proinsulin either in cases or in controls.

A multiple regression analysis was performed to study the effect of possible predictors on HDL-cholesterol and LDL-cholesterol. On a univariate analysis, lower HDL-cholesterol levels were associated with male gender, a positive family history of DM, higher BMI, waist to hip ratio and triglyceride levels. On a multivariate analysis, lower HDL levels were associated with male gender, a positive family

Table 4. Correlation of lipid levels with area under the curves of insulin, glucose and proinsulin

	Triglycerides		Total cholesterol		HDL-cholesterol		LDL-cholesterol	
Area under the curve	Cases r (P value)	Controls r (P value)	Cases r (P value)	Controls r (P value)	Cases r (P value)	Controls r (P value)	Cases r (P value)	Controls r (P value)
Insulin (nmol/l min^{-1})	0.095 (0.313)	0.354 (<0.001*)	0.254 (0.01*)	0.176 (0.06)	-0.006 (0.95)	-0.098 (0.30)	0.233 (0.013*)	0.099 (0.297)
Glucose (mmol/l min^{-1})	0.186 (0.05*)	0.222 (0.02*)	0.034 (0.72)	0.173 (0.06)	-0.127 (0.18)	-0.013 (0.89)	-0.005 (0.96)	0.113 (0.23)
Proinsulin (nmol/l min^{-1})	0.201 (0.056)	0.323 (0.003*)	0.211 (0.044*)	0.020 (0.85)	-0.099 (0.348)	0.024 (0.85)	0.150 (0.07)	-0.100 (0.36)

HDL: high density lipoprotein; LDL: low density lipoprotein.
*Significant at 0.05 level.

Table 5. Multiple regression analysis of HDL-cholesterol

	Univariate			Multivariate		
Parameter	β	SE	P value	β	SE	95% CI
Age (years)	0.001	0.002	0.558			
Sex (male=1 / female=2)	0.110	0.034	0.001	0.070	0.034	0.003 to 0.138
BMI (kg/m^2)	-0.017	0.005	0.002			
Family history of DM (yes=1 / no=0)	-0.121	0.033	<0.001	-0.107	0.032	-0.170 to -0.045
AUC insulin (nmol/l min^{-1})	-0.008	0.008	0.329			
AUC glucose (mmol/l min^{-1})	-0.205	0.179	0.254			
Waist to hip ratio x 100	-0.009	0.002	<0.001	-0.006	0.003	-0.011 to -0.001
Triglycerides (mmol/l)	-0.102	0.027	<0.001	-0.069	0.027	-0.122 to -0.015

β: regression coefficient; SE: standard Error; CI: confidence interval; DM: diabetes mellitus; AUC: area under the curve; BMI: body mass index.

history of DM, higher BMI, waist to hip ratio and triglyceride (Table 5). On a univariate analysis, a higher LDL-cholesterol was associated with higher age ($p < 0.001$), BMI ($p < 0.001$) and waist to hip ratio ($p = 0.002$). On a multivariate analysis, higher LDL-cholesterol levels were associated with age and BMI only. Even though LDL-cholesterol was a derived parameter, serum LDL level did not show any significant correlation with serum TG or HDL levels.

DISCUSSION

Behavioral and pharmacological interventions in high risk groups can reduce the number of individuals who develop DM by 25-60%.[22-24] As a result, discussions on mitigating the growing public health problem of type 2 DM have expanded from a relatively narrow focus on disease treatment to broader focus on disease prevention.[25] The San Antonio Heart Study (Mexican American, non-Hispanic population) has reported higher prevalence of atherogenic risk factors, including high BMI, high systolic and diastolic blood pressure, high TG and low HDL concentrations in subjects with family history of type 2 DM.[26] The study population included a large number of subjects with impaired glucose tolerance, impaired fasting glucose and obesity. After adjustment for insulin, BMI and waist to hip ratio, the effect of parental history of diabetes on dyslipidemia was not significant.[26]

Parental history of type 2 DM was associated with higher waist to hip ratio and a lower HDL-cholesterol in pre-pubertal Malay children.[27] Tan et al in a study of South East Asian populations, which included Chinese, Malay and Asian Indians, observed higher BMI and low HDL-cholesterol among subjects with a family history of type 2 DM,[28] whereas TG levels and total cholesterol levels were not significantly different.[28] Anjana et al also observed that adolescents who had parents with diabetes had lower HDL and higher BMI compared to those whose parents did not have DM.[29] Psyrogiannis et al studied lipid levels among Caucasian subjects of Greek origin with a mean age of about 42 years. Serum TG, total cholesterol, LDL-cholesterol and Lp(α) were significantly higher and HDL was significantly lower in offspring of diabetic parents compared to subjects whose parents did not have DM.[30] In this study the mean BMI in both groups was in the overweight range.[30] Groop et al found that non-diabetic males with a family history of DM had higher BMI, fasting glucose and triglycerides compared to males without family history of DM. Non-diabetic females with family history of DM had higher BMI, HbA1C and diastolic blood pressure and lower HDL-cholesterol.[31] Tian et al compared type 2 diabetics and their first degree relatives with healthy controls without family history of diabetes among Han Chinese origin participants.[32] In this study the first degree relatives had higher mean BMI and lower mean age compared to normal controls. Statistical significance was not mentioned. The first degree relatives had significantly higher TG, lower HDL-cholesterol and higher post prandial C-peptide levels compared to controls, whereas no significant difference in fasting and post prandial insulin, fasting C-peptide, waist to hip ratio, systolic and diastolic blood pressure was disclosed.[32]

Low HDL-cholesterol values along with overweight and glucose intolerance in offspring of diabetics is well documented. However, it is not clear whether the low HDL is an effect of glucose intolerance/overweight or genetic background of diabetes itself. We studied normal weight offspring of diabetics who had normal glucose tolerance and gender matched controls of comparable age without family history of DM. The mean BMI of the cases and controls were 20.8 and 20.2, respectively. The age ranged from 5 to 53 years (mean for cases and controls were 24 and 24.1 years, respectively). The waist to hip ratio, glucose levels at different time points of an OGTT and the area under the curve of glucose were comparable in the two groups. There was no significant difference in TG and total cholesterol levels between cases and controls. HDL-cholesterol levels were significantly lower in offspring of diabetics compared with controls. TG to HDL ratio was also significantly higher in cases. The number of subjects with low HDL-cholesterol was higher in cases compared to controls. HDL-cholesterol levels showed no significant correlation with area under the curves of insulin, glucose and proinsulin either in cases or controls. Nevertheless, the higher insulin levels (AUC during GTT) in cases are possibly of clinical relevance.

Several earlier studies have suggested that insulin resistance may be a factor causing dyslipidemia.[33-35]

The characteristic lipoprotein abnormalities associated with insulin resistance include hypertriglyceridemia, low HDL-cholesterol and low apolipoprotein A-1.[33-36] In the present study, insulin resistance as measured by HOMA-IR and whole body insulin sensitivity index was not different between offspring of diabetics and controls. However, the area under the curve of insulin, proinsulin and ratio of area under the curves of proinsulin to C-peptide were higher among offspring of diabetics compared to controls. Several earlier studies have shown that abnormalities of lipoproteins, low HDL and high proinsulin are independent risk factors for the prediabetic state.[37-40]

Population studies have shown that HDL-cholesterol is a strong, independent inverse predictor of cardiovascular disease.[41,42] The protective effect of HDL-cholesterol is considered to be due to its effects in reversing cholesterol transport, inflammation, apoptosis, etc.[43] Studies in experimental animals have shown that lipoproteins modulate the function and survival of insulin secreting cells. Purified human VLDL and LDL particles reduce insulin mRNA levels and β-cell proliferation, while there is a dose-dependent increase in the rate of apoptosis.[44] The inhibitory effects of LDL on insulin secretion and beta cell proliferation have also been shown in primary human islets,[45] while HDL was found to modulate the survival of both human and murine islets. Moreover, HDL antagonizes the glucose and interleukin-1beta induced apoptosis.[45] The pro-apoptotic signals of LDL and VLDL were antagonized by HDL particles. Two components of HDL, apolipoprotein A1 and sphingosine-1-phosphate (S1P), were found to protect beta cell from cytokine and glucose induced apoptosis.[45] Bezafebrate treatment, which raises HDL-cholesterol levels by 16%, decreased TG levels by 24%, reduced the incidence and delayed the onset of type 2 DM in coronary artery disease patients with impaired fasting glucose.[46] This raises the question whether low HDL-cholesterol contributes to beta-cell failure and the manifestation/progression of type 2 diabetes mellitus. A recent study has documented that raising plasma HDL level with reconstituted HDL infusion leads to reduced plasma glucose, increased plasma insulin and enhanced beta cell function in patients with type 2 DM.[47]

We conclude that plasma HDL-cholesterol in offspring of subjects with type 2 DM is low in the absence of overweight, obesity and glucose intolerance. This finding may have implications in diabetes mellitus/cardiovascular disease prevention programmes.

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Disclosure

None.

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