β -Blockers, lipoproteins and non-insulin dependent diabetes

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Summary: In a study on 138 hypertensive non-insulin dependent diabetic subjects, factors influencing lipoproteins were assessed. Multiple regression analyses were carried out in order to assess the influence of β -blocker antihypertensive therapy while making allowances for other confounding variables. In males, but not in females, on a β -blocker for hypertension, total high density lipoprotein- (HDL-) and HDL-subfraction cholesterol were significantly lower while the serum triglyceride was increased, though not significantly. In male non-insulin dependent diabetics, regimens containing a β -blocker may worsen an already abnormal lipoprotein profile and antihypertensive agents other than β -blocking agents should be used if possible.

Introduction

As the incidence of coronary heart disease is greatly increased in non-insulin dependent diabetes,¹ abnormalities of plasma lipoproteins in diabetes may be a key causal factor because of the established association between alterations in lipoproteins and the development of vascular disease.²

In the general population antihypertensive therapy has been shown to affect lipoproteins, in particular the β -adrenergic blocking agents where there is often an associated elevation in serum triglyceride and a lowering of HDL-cholesterol (HDL-C).³ To date the influences of the antihypertensive agents on lipoproteins in the diabetic have not been so clearly evaluated. In contrast to the non-diabetic, the uncomplicated non-insulin dependent diabetic commonly has an elevated serum triglyceride and a low HDL-C.⁴ Due to the high prevalence of hypertension in non-insulin dependent diabetes,⁵ blood pressure lowering agents are frequently used. It was therefore of interest to assess if these drugs could potentially worsen existing abnormalities in serum lipids and lipoproteins in non-insulin dependent diabetes. The aim of this study was to assess if the addition of a β -adrenergic blocking agent as a part of blood pressure lowering therapy had an influence on the lipid and lipoprotein profile of stable hypertensive non-insulin dependent diabetic subjects.

Patients and methods

One hundred and thirty-eight (71 male and 67 female) hypertensive non-insulin dependent diabetic subjects were assessed in the St Mary's Hospital Diabetic Clinic. All subjects were aged 45-75 years and had been treated for non-insulin diabetes for at least one year. No subject gave a history of ketosis. Diabetic therapy consisted of either diet alone or in combination with an oral hypoglycaemic agent (Table I). Hypertension was defined as being on antihypertensive therapy for at least 6 months. Age, past medical history, antihypertensive medication, alcohol and tobacco consumption were recorded on a standardized questionnaire (Table I). The hypertensive patients were divided into two groups. The first group included those whose therapy consisted of a β -blocker either alone or in combination with other anti-hypertensive agents. In 63% of males and 79% of females β -blocker therapy included a β_1 -selective agent. Other β -blockers included either a non-selective agent or a β -blocker with intrinsic sympathomimetic activity. In the second group, patients received other antihypertensive agents, but no β -blocker. No patient had liver or renal impairment (creatinine $\geq 140 \mu\text{mol/l}$) and none had persistent proteinuria. No patient was on hormone replacement therapy or lipid modifying therapy. Height and weight were recorded for body mass index calculations (weight in kg/height in m^2). Fasting blood samples were taken for the measurement of glucose, haemoglobin (Hb) A₁, C-peptide, insulin, triglyceride, cholesterol, HDL-cholesterol and HDL-subfraction cholesterol.

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Table I Characteristics of hypertensive diabetic groups

	β -blocker	No β -blocker
Male ($n=71$)	($n=41$)	($n=30$)
Age (y)†	59.7 (± 6.8)	64.3 (± 9.2)*
Obesity (BMI)†	27.9 (23.2–36)	25.8 (20.9–32.8)
Current smokers	9 (22%)	12 (40%)**
No. teetotal	18 (44%)	12 (40%)
Duration of diabetes† (y)	7 (1–21)	8 (1–30)
Treatment for diabetes:		
Diet alone	13 (32%)	5 (17%)
Diet + hypoglycaemic agent	27 (68%)	26 (87%)
Female ($n=67$)	($n=38$)	($n=29$)
Age (y)†	60.8 (± 7.6)	60.0 (± 8.6)
Obesity (BMI)†	29.7 (22.4–42.7)	28.1 (19.9–37.4)
Current smokers	7 (18%)	2 (7%)
No. teetotal	26 (68%)	21 (70%)
Duration of diabetes† (y)	5 (1–23)	6 (1–23)
Treatment for diabetes:		
Diet alone	13 (32%)	5 (17%)
Diet + hypoglycaemic agent	27 (68%)	26 (87%)

†Mean ($\pm$ s.d.); †median (range)* $P < 0.05$; ** $P < 0.01$.

Laboratory methods

Plasma glucose was measured enzymatically using a Glucoroder (Ultralab) and glycosylated haemoglobin by Corning gel electrophoresis. Serum cholesterol and triglyceride were analysed enzymatically using Boehringer reagents on a Centrifichem centrifugal analyser (Baker Instruments). Total HDL- and HDL₃-cholesterol were measured following selective precipitation of other lipoproteins with dextran sulphate-magnesium chloride.^{6,7} HDL₂-cholesterol was calculated by subtraction. LDL was calculated using the Friedewald equation⁸ and only the results of subjects with a triglyceride of <4.6 mmol/l were reported.

Statistical methods

Data were analysed using the SAS Statistical Package at the University of London Computer Centre. Because of the skewed distribution of weight, plasma glucose, triglyceride, HDL₂-cholesterol, C-peptide, insulin and duration of diabetes, these parameters were log transformed to yield approximately normal distributions. Univariate comparisons between treatment groups were analysed using the unpaired *t*-test and multiple regression was used to assess the influence of combinations of the variables age, obesity, history of tobacco and alcohol consumption, β -blockers, triglyceride, C-peptide and blood glucose, on lipids and lipoproteins. Male and female subjects were analysed separately.

Results

In the male subjects of this study, duration of diabetes and the percentage of drinkers were similar, but there were fewer smokers in the β -blocker group (Table I). However, those treated with a β -blocker, compared to those not on a β -blocker were younger and slightly, but not significantly, heavier than those not on β -blockers (Table I). Indices of glycaemic control (fasting blood glucose, HbA_{1c}), C-peptide, insulin, total and LDL-cholesterol, were similar in both treatment groups (Table II). In males treated with a β -blocker, HDL-C, HDL₂-cholesterol and HDL₃-cholesterol were significantly lower than in the group not on a β -blocker (Table II). Serum triglyceride was slightly increased in the β -blocker group. In multiple regression analysis, β -blockers were the most significant ($P < 0.001$) variables associated with a low HDL-, HDL₂- and HDL₃-cholesterol when allowing for age, obesity, smoking and alcohol (Table III). When a further analysis of these variables was performed for triglyceride, β -blockers, as well as obesity, had the most significant association. There was also a weak inverse association of alcohol with HDL₂-cholesterol concentrations. When triglyceride, C-peptide and blood glucose were added as variables to the model, the presence of β -blocker therapy and the triglyceride concentration emerged as the most significant factors associated with a low HDL-C, HDL₂-C and HDL₃-C (Table IV).

For the females, both treatment groups were

Table II Biochemical variables in male hypertensive diabetics

	β -blocker (n = 41)	No β -blocker (n = 30)
Blood glucose†	9.7 (4.3–20.7)	8.2 (4–17.2)
HbA _{1c} (%)	9.9 ($\pm$ 2.3)	9.5 ($\pm$ 2.4)
C-peptide (mU/l)†	2.4 (0.8–6.1)	1.9 (0.4–6.6)
Insulin (mU/l)	7.8 (2.7–34.8)	6.6 (<0.3–24.5)
Cholesterol (mmol/l)	5.8 ($\pm$ 0.9)	5.9 ($\pm$ 0.9)
LDL-C (mmol/l)	[n = 38] 3.9 ($\pm$ 0.9)	4.0 ($\pm$ 0.9)
Triglyceride (mmol/l)†	1.9 (0.6–7.4)	1.4 (0.5–2.2)
HDL-C (mmol/l)	0.89 ($\pm$ 0.25)	1.24 ($\pm$ 0.39)***
HDL ₂ -C (mmol/l)†	0.17 (0.02–0.51)	0.26 (0.5–1.39)**
HDL ₃ -C (mmol/l)	0.70 ($\pm$ 0.16)	0.85 ($\pm$ 0.20)**

Values given are mean ($\pm$ s.d.) except † = median (range).
 $P < 0.06$; ** $P < 0.01$; *** $P < 0.001$.

Table III Associations of lipid and lipoprotein determinants in males (multiple regression)

	HDL-C	HDL ₂ -C	HDL ₃ -C	Triglyceride
Age	(–) $P < 0.05$	(–) $P < 0.01$	NS	NS
Obesity (BMI)	(–) $P < 0.05$	(–) $P < 0.01$	NS	(+) $P < 0.001$
Smoking	NS	(–) $P < 0.05$	NS	NS
Alcohol	NS	(–) $P < 0.05$	NS	(+) $P < 0.05$
β -blockers	(–) $P < 0.001$	(–) $P < 0.001$	(–) $P < 0.01$	(+) $P < 0.001$

NS = not significant; (+) = positive association; (–) = inverse association.

similar in age, duration of diabetes, alcohol consumption and obesity, while the β -blocker group had slightly increased number of smokers (Table I). In both groups indices of glycaemic control (fasting blood glucose, HbA_{1c}), C-peptide, insulin,

Table IV Associations of determinants of HDL in males (multiple regression)

	HDL-C	HDL ₂ -C	HDL ₃ -C
Age	(–) $P < 0.05$	(–) $P < 0.01$	NS
Obesity (BMI)	NS	NS	NS
Smoking	NS	(–) $P < 0.05$	NS
Alcohol	NS	NS	NS
β -blockers	(–) $P < 0.001$	(–) $P < 0.01$	(–) $P < 0.01$
Triglyceride	(–) $P < 0.001$	(–) $P < 0.001$	(–) $P < 0.01$
C-peptide	NS	NS	NS
Blood glucose	NS	NS	(+) $P < 0.01$

NS = not significant; (+) = positive association; (–) = inverse association.

total and LDL-cholesterol were similar (Tables II and V). In females serum triglyceride was higher and total HDL- and HDL₂-cholesterol were lower in the β -blocker group, but these differences were not statistically significant (Table V). In multiple regression with triglyceride, C-peptide and blood glucose in the model only triglyceride had significant associations with a low HDL-C ($P < 0.001$), HDL₂-C ($P < 0.001$) and HDL₃-C ($P < 0.001$).

Discussion

This study has shown that male hypertensive non-insulin dependent diabetic subjects on a β -blocker had a significantly lower HDL and subfraction cholesterol than those not so treated. Females treated with a β -blocker had similar changes in lipoproteins, but these were not statistically significant.

Factors known to influence HDL such as glycaemic control^{9,10} duration of diabetes,^{9,10} renal failure^{10,11} dietary or exercise change^{10,11} and lipid modifying or hormone therapy^{10,11} were accounted

Table V. Biochemical variables in female hypertensive diabetics

	β-blocker (n = 38)	No β-blocker (n = 29)
Blood glucose†	9.7 (5.8–26.0)	10.6 (4.8–18.4)
HbA _{1c} (%)	10.8 (± 2.6)	10.9 (± 2.3)
C-peptide (mU/l)†	2.2 (0.8–6.8)	2.1 (0.6–6.0)
Insulin (mU/l)	8.4 (2.6–89.4)	9.5 (3.1–35.2)
Cholesterol (mmol/l)	6.28 (± 1.15)	6.05 (± 0.98)
LDL-C (mmol/l)	[n = 36] 4.30 (± 1.05)	[n = 28] 4.10 (± 0.97)
Triglyceride (mmol/l)†	1.61 (0.77–5.25)	1.22 (0.43–6.80)
HDL-C (mmol/l)	1.18 (± 0.31)	1.24 (± 0.38)
HDL ₂ -C (mmol/l)†	0.22 (0.07–0.86)	0.37 (0.07–0.84)
HDL ₃ -C (mmol/l)	0.89 (± 0.19)	0.86 (± 0.21)

Values given are mean (± s.d.) except † = median (range).

for in the selection of stable diabetic subjects or were matched in the two treatment groups.

The increased frequency of cigarette smokers in the males without a β-blocker would have favoured a lower HDL-C in this group.^{11,12} This effect may have been offset by the differences in the two groups in the degree of obesity, another important determinant of a low HDL.^{10,11,13} It was of interest that although the β-blocker group were heavier this was not significant on univariate analysis. However in multiple regression of major determinants of HDL which included obesity, alcohol,^{11,14} tobacco, β-blockers³ as well as age, β-blockers in this diabetic study emerged as the most significant factor associated with a low HDL and subfraction cholesterol. In a further analysis of these variables with respect to triglyceride, β-blockers again, as well as obesity, emerged as the most significant factor (Table IV). Due to the metabolic associations of triglyceride,¹⁵ C-peptide,¹⁶ blood glucose⁹ and HDL these parameters were also included in the model. β-blockers were again significant, however the strong inverse association of triglyceride and HDL was also shown.

In this study there appeared to be an inverse association of alcohol with the HDL₂-subfraction (Table III). In the non-diabetic, alcohol has been associated with a raised HDL-cholesterol and whether this is due to alterations in HDL₂ or HDL₃ is at present unclear.^{10,11,14} However, our results would suggest that alcohol influences on lipoproteins in the hypertensive diabetic subject may differ from those seen in the non-diabetic.

The exact mechanism whereby β-blocker therapy is associated with a raised triglyceride and low HDL-C is not clear. It is possible that β-adrenergic blocking agents exert their influence on lipid metabolism at several physiological sites. Adrenergic

mechanisms and hence adrenergic blocking agents may influence factors important in endogenous lipoprotein production such as glucose, insulin, free fatty acid concentrations as well as esterification and secretion processes.¹⁷ Lipoprotein secretion patterns from both liver and gut may be altered by blood flow changes as a consequence of anti-hypertensive drug action.¹⁷ β-blockers could also exert their action on serum lipids through the enzyme lipoprotein lipase. This enzyme located on the capillary endothelium is involved in the intra-vascular lipolysis of triglyceride-rich lipoproteins. During this process 'mature' HDL is formed. Alteration of vascular tone could affect the delivery of triglyceride-rich lipoproteins to the endothelial lipase as well as altering the endothelial surface area for lipase binding sites.¹⁷ A direct reduction in lipoprotein lipase activity by β-adrenergic blocking agents producing unopposed α-adrenergic inhibition of the enzyme has previously been documented.¹⁸ However, the synthesis of lipoprotein lipase and its translocation to the endothelial surface have been shown to be under adrenergic control.¹⁹ Thus, reduction in lipoprotein lipase activity would appear to be one of the important sites whereby these drugs induce an increased triglyceride and low HDL. However from this study, as total and subfraction HDL-cholesterol were both reduced, an increase in hepatic removal processes, either receptor-mediated or by altered hepatic endothelial lipase activity,¹⁷ must also be considered.

In this assessment of diabetic subjects all classes of β-blockers were analysed together, as all classes of β-blockers in the non-diabetic have produced similar alterations in triglyceride concentrations and most lower HDL- and subfraction cholesterol.³

The most consistent lipoprotein abnormality in the chronic stable non-insulin dependent diabetic is a raised triglyceride and low HDL-cholesterol. As

there is a relationship between low HDL-cholesterol and large vessel disease in the non-insulin dependent diabetic,^{4,20} the further lowering of this lipoprotein by a commonly used antihypertensive agent may be detrimental to subjects who already have a greater risk of macro-vascular complications com-

pared to the non-hypertensive diabetic.

We conclude from this study that in the male, and possibly in female, non-insulin dependent diabetic, β -adrenergic blocking agents should be avoided, if possible, in the treatment of their hypertension.

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