Relationship Between Plasma Insulin Levels and High Density Lipoprotein Cholesterol Levels in Healthy Men

M. Stalder, D. Pometta and A. Suenram

Division de Diabetologie, Hôpital Cantonal Universitaire, Geneva, Switzerland

Summary. Insulin and high density lipoproteins are considered to play a role in the development of atherosclerosis. In order to study whether there was a relationship between endogenous plasma insulin response and high density lipoproteins, an acute intravenous glucose tolerance test (0.5 g glucose/kg body weight) was performed in 94 healthy men, aged 20–49 years. Cholesterol and triglyceride levels were measured in very low density lipoproteins, low density lipoproteins and high density lipoproteins isolated from fasting serum by preparative ultracentrifugation. The subjects were divided into quartiles according to their fasting and post-glucose load plasma insulin and high density lipoprotein cholesterol levels. The results obtained in the subjects of the upper quartiles were compared with the results obtained in the subjects of the lower quartiles. The mean glucose disappearance rates were within the normal range and did not differ between the upper and lower quartiles. Subjects with high fasting plasma insulin had lower high density lipoprotein cholesterol levels (1.11 ± 0.34 mmol/l, $p = 0.01$) than men with low fasting plasma insulin (1.40 ± 0.37 mmol/l). Higher mean post-glucose plasma insulin was associated with lower high density lipoprotein cholesterol levels (1.18 ± 0.32 mmol/l, $p < 0.05$) and increased high density lipoprotein triglyceride levels (0.14 ± 0.07 mmol/l, $p < 0.01$) when compared with the men with low post-glucose plasma insulin (1.40 ± 0.36 mmol/l and 0.09 ± 0.03 mmol/l respectively). These observations reflect the close relationship between endogenous insulin and lipoprotein metabolism.

Key words: Plasma insulin, lipoproteins, HDL cholesterol, intravenous glucose tolerance test.

Low high density lipoprotein (HDL) cholesterol is associated with coronary heart disease [1–7] and has a better predictive value for the occurrence of myocardial infarction than low density lipoprotein (LDL) cholesterol [5, 6]. The ‘favourable effect’ of HDL cho-

lesterol has been related to tissue cholesterol transport and competitive action at the LDL surface cell receptors [8–10]. In previous studies, we demonstrated that the first degree relatives of patients who have had acute myocardial infarction had lower HDL cholesterol than control subjects [11, 12] and that low HDL cholesterol was demonstrable even in children [13].

The prevalence of hyperlipoproteinaemia and coronary heart disease is high among diabetics but is not related to the severity of diabetes measured by the degree of insulin dependence [14–17]; indeed, latent diabetics may have severe cardiovascular disease [18]. Overt diabetics, both insulin dependent or independent, have been shown to have low HDL cholesterol [19–22], which could possibly be considered as a cardiovascular risk factor. During insulin therapy, a rise in HDL cholesterol has been observed [23], suggesting that improved diabetic control may decrease the risk of ischaemic heart disease [24]. Contradictory results have been found by others [25, 26].

The purpose of the present study was to investigate whether in a healthy population there was a relationship between HDL cholesterol and endogenous plasma insulin. The subjects were divided into quartiles on the basis of fasting insulin, insulin after an intravenous glucose challenge and HDL cholesterol. Comparisons were made between the subjects of the upper and lower quartiles with special attention to the lipoprotein, cholesterol and triglyceride levels.

Subjects and Methods

The subjects of the present study were men (aged 20–49 years) randomly selected from an apparently healthy population who participated in Geneva in the study ‘Serum lipoproteins in four European communities’ [27]. The following predetermined grounds for exclusion were employed to define the healthy population: (a) Clinical and ECG evidence of ischaemic heart disease, and evidence of peripheral vascular disease from history and clinical examination. (b) Known diabetes mellitus or fasting plasma glucose (≥ 8.0 mmol/l) [18]. (c) Cirrhosis of the liver, chronic renal failure, and malignant disease. (d) Adherence to therapeutic diets (e. g. weight-reducing or diabetic diets), the taking of drugs known to affect lipid or carbohy-

Table 1. Comparison between subjects selected according to the fasting insulin quartiles

	Fasting insulin (IRI)			
	Quartile I (1–6.9 mU/l)	Quartile II (7–10.9 mU/l)	Quartile III (11–17.9 mU/l)	Quartile IV (18–43 mU/l)
Serum cholesterol (mmol/l)	5.48 ± 1.0	5.34 ± 0.94	5.34 ± 1.2	5.53 ± 1.17
Serum triglycerides (log)	0.029 ± 0.302	−0.045 ± 0.173	−0.006 ± 0.235	0.153 ± 0.326
(antilog) (mmol/l)	1.07	0.90	0.98	1.42
HDL cholesterol (mmol/l)	^a 1.40 ± 0.37	1.34 ± 0.36	1.24 ± 0.32	1.11 ± 0.34
HDL triglycerides (mmol/l)	0.11 ± 0.05	0.11 ± 0.05	0.11 ± 0.05	0.14 ± 0.07
LDL cholesterol (mmol/l)	3.07 ± 0.68	3.22 ± 0.76	3.25 ± 0.89	3.26 ± 0.89
VLDL cholesterol (log)	−0.393 ± 0.406	−0.464 ± 0.217	−0.425 ± 0.287	−0.274 ± 0.373
(antilog) (mmol/l)	0.40	0.34	0.38	0.53
VLDL triglycerides (log)	−0.226 ± 0.425	−0.314 ± 0.248	−0.273 ± 0.358	−0.069 ± 0.419
(antilog) (mmol/l)	0.59	0.49	0.53	0.85
Fasting glucose (mmol/l)	5.11 ± 0.36	5.07 ± 0.52	5.21 ± 0.54	5.34 ± 0.86
K (%/min)	1.60 ± 0.51	1.95 ± 0.81	1.68 ± 0.43	1.68 ± 0.58
Weight index	0.97 ± 0.09	0.97 ± 0.11	1.01 ± 0.13	1.03 ± 0.13

Results are expressed as mean ± SD. K: disappearance rate of glucose/min. Comparison between quartiles I and IV: ^a*p* = 0.01

drate metabolism and a known change in body weight of more than 1.5 kg in the previous month. (e) Major acute illness, surgery or trauma within the previous 3 months.

Subjects attended the clinic on a weekday morning before work. Informed consent was obtained verbally from each subject before entering the study. The investigation included a medical history, physical examination and an ECG. Height and weight were recorded and the height/weight index derived:

$$\frac{\text{weight (kg)}}{\text{height (cm)} - 100}$$

The subjects were asked to return to the clinic for an IV glucose tolerance test. They had been carefully instructed to eat at least 300 g of carbohydrates daily during the 3 days preceding the test and to fast for 12–14 h before the test. Venous blood was drawn in the fasting state for lipid analyses on whole serum and in the three major lipoprotein classes: VLDL, LDL and HDL. Cholesterol in whole serum and lipoproteins was measured after hydrolysis with ethanolic KOH and nonane extraction followed by the Liebermann-Burchard reaction [28]. Serum triglyceride levels were determined according to Soloni [29]. Lipoproteins were separated after preparative ultracentrifugation. The recovery and precision of the method were previously reported [11].

Plasma glucose was measured by enzymatic method (hexokinase) [30] and immunoreactive insulin (IRI) was measured using the Phadebas Pharmacia kit [31].

The IV glucose tolerance test was performed with 0.5 g glucose (40%)/kg body weight injected in less than 5 min. The disappearance rate of glucose/min (K) was determined graphically according to Amatuzio et al. [32]. Plasma glucose was determined before the test and after 10, 20, 30, 40, 50 and 60 min. IRI measurements were made at 0, 4, 6, 8, 10, 30 and 60 min after the load in order to evaluate both the early and the late insulin secretion.

Alcohol consumption, cigarette smoking and physical activity were assessed by questioning during the medical examination. The alcohol consumption was expressed as litres of wine (10°) per week as the use of wine is more widespread than other alcohols in the Geneva area. Beers and hard liquors consumed were therefore transformed into wine 'equivalents' on the basis of pure alcohol content.

The statistical analysis of the differences between means of two samples was performed using the Student's *t* test. Before calculation, serum and VLDL triglyceride levels as well as VLDL cholesterol were transformed to their logarithms. The Chi square test was

used to compare the proportion of smokers, alcohol consumers and subjects with high or low physical activity both at work and at leisure between the samples studied.

Results

A total of 482 men entered the study, 14 of whom were excluded according to the predetermined grounds. One was an overt diabetic. From the remaining 468 men, 94 were randomly selected for the present study.

The results were analysed using quartiles defined according to insulin and to HDL cholesterol levels. The comparison was made between the lower (I) and upper (IV) quartiles but the results in the intermediate quartiles (Table 1) are consistent with the results of the lower and upper quartiles.

Fasting Plasma Insulin

Subjects with high fasting plasma insulin (quartile IV) had significantly lower HDL cholesterol (1.11 ± 0.34 mmol/l, mean ± SD, *p* = 0.01) than subjects with low fasting insulin (1.40 ± 0.37 mmol/l; Table 1). No differences could be found in fasting blood glucose or K values which were within normal range.

Plasma Insulin After Glucose Load

When the mean plasma insulin after glucose load was used to separate the low insulin responders (quartile I) and the high insulin responders (quartile IV) it appeared (Table 2) that high plasma insulin response was associated with low fasting HDL cholesterol (1.18 ± 0.32 versus 1.40 ± 0.36 mmol/l; *p* < 0.05). High plasma insulin in response to glucose load was also associated with higher fasting HDL trigly-

cerides (0.14 ± 0.07 versus 0.09 ± 0.03 mmol/l; $p < 0.01$) and increased body weight index (1.04 ± 0.13 versus 0.95 ± 0.10 ; $p < 0.05$).

There was no difference in the mean glucose or K values after the glucose challenge between the two quartiles.

HDL Cholesterol and Plasma Insulin

When the subjects were stratified according to their HDL cholesterol it appeared (Table 3) that low HDL cholesterol (quartile I) was associated with high plasma insulin both fasting (16.6 ± 11.0 mU/l) and after glucose load (41.5 ± 20.9 mU/l, $p < 0.01$). The subjects with high HDL cholesterol (quartile IV) had lower fasting IRI (9.1 ± 5.7 mU/l) and lower IRI after glucose load (27.1 ± 14.4 mU/l, $p = 0.01$).

Low HDL cholesterol was also associated with higher VLDL triglycerides (1.03 versus 0.35 mmol/l, $p < 0.001$) and greater body weight index (1.03 ± 0.10 versus 0.97 ± 0.11 , $p < 0.05$).

Cigarette Smoking, Alcohol Consumption and Physical Activity

No significant differences were found in cigarette smoking, alcohol consumption and physical activity either at work or at leisure between the quartiles under study.

Description of the Population

The mean values and standard deviations of the different variables studied for the entire population (94 men) are given in Table 4.

Discussion

From the present data, it appears that in contrast to previous observations by Enger and Erikssen [33] who found no correlation between fasting insulin and HDL cholesterol, the subjects with the highest fasting plasma insulin concentrations have lower HDL cholesterol when compared to subjects with lower fasting insulin who have higher HDL cholesterol.

High plasma insulin and low HDL cholesterol levels occur in obesity [5, 6, 34]. High fasting plasma insulin and low HDL cholesterol could therefore be related to obesity. However the mean body weight index of the group of subjects selected for their high fasting plasma insulin was within normal range and did not differ significantly from the body weight index of the subjects with low fasting insulin. The association of high fasting insulin and low HDL cholesterol is therefore not related to obesity.

When the plasma insulin levels measured after the glucose load are considered, it appears that similarly to what was observed at the fasting stage, the subjects

Table 2. Comparison between subjects with low (quartile I) and high (quartile IV) mean plasma insulin after IV glucose challenge

	Mean plasma insulin (IRI) after IV glucose	
	Quartile I (9–21 mU/l)	Quartile IV (44–95 mU/l)
Serum cholesterol (mmol/l)	5.35 ± 0.80	5.46 ± 1.26
Serum triglycerides (log)	-0.067 ± 0.194	0.059 ± 0.265
(antilog) (mmol/l)	0.86	1.15
HDL cholesterol (mmol/l)	$^a 1.40 \pm 0.36$	1.18 ± 0.32
HDL triglycerides (mmol/l)	$^b 0.09 \pm 0.03$	0.14 ± 0.07
LDL cholesterol (mmol/l)	3.21 ± 0.63	3.28 ± 0.94
VLDL cholesterol (log)	-0.535 ± 0.267	-0.378 ± 0.326
(antilog) (mmol/l)	0.29	0.42
VLDL triglycerides (log)	-0.354 ± 0.315	-0.179 ± 0.345
(antilog) (mmol/l)	0.44	0.66
Mean post-load glucose (mmol/l)	11.96 ± 1.67	11.95 ± 1.79
K (%/min)	1.58 ± 0.50	1.80 ± 0.50
Weight index	$^a 0.95 \pm 0.10$	1.04 ± 0.13

$^a p < 0.05$ $^b p \leq 0.01$. K = disappearance rate of glucose/min

Table 3. Comparison between subjects with low (quartile I) and high (quartile IV) HDL cholesterol

	HDL cholesterol	
	Quartile I (< 1.02 mmol/l)	Quartile IV (> 1.48 mmol/l)
Fasting IRI (mU/l)	$^b 16.6 \pm 11.0$	9.1 ± 5.71
Mean IRI after IV glucose (mU/l)	$^b 41.5 \pm 20.93$	27.1 ± 14.41
HDL triglycerides (mmol/l)	0.13 ± 0.07	0.11 ± 0.04
VLDL triglycerides (log)	$^c 0.014 \pm 0.408$	-0.458 ± 0.349
(antilog) (mmol/l)	1.03	0.35
LDL cholesterol (mmol/l)	3.02 ± 0.61	3.24 ± 0.69
K (%/min)	1.66 ± 0.48	1.55 ± 0.43
Weight index	$^a 1.03 \pm 0.10$	0.97 ± 0.11

$^a p < 0.05$ $^b p \leq 0.01$ $^c p < 0.001$. K = disappearance rate of glucose/min

Table 4. The different variables for the 94 men studied (mean $\pm$ SD)

Fasting IRI (mU/l)	13 $\pm$ 8.6
Mean IRI after IV glucose (mU/l)	34 $\pm$ 18.5
Serum cholesterol (mmol/l)	5.41 ± 1.05
Serum triglycerides (log)	0.028 ± 0.267
(antilog) (mmol/l)	1.07
HDL cholesterol (mmol/l)	1.28 ± 0.36
HDL triglycerides (mmol/l)	0.12 ± 0.06
LDL cholesterol (mmol/l)	3.21 ± 0.80
VLDL cholesterol (log)	-0.394 ± 0.325
(antilog) (mmol/l)	0.40
VLDL triglycerides (log)	-0.226 ± 0.369
(antilog) (mmol/l)	0.59
Fasting glucose (mmol/l)	5.18 ± 0.59
K (%/min)	1.74 ± 0.62
Weight index	1.0 ± 0.11

K = disappearance rate of glucose/min

with high plasma insulin response have low HDL cholesterol levels. These results are in agreement with the observation by Enger and Erikssen [33] that high post glucose load plasma insulin was associated with low HDL cholesterol levels. However the mean body weight index of their subjects with high post glucose insulin levels was 1.10 and different from 0.96 for their subjects with low insulin response. The influence of obesity in their observations can therefore not be ruled out. In the present study, the men with high plasma insulin after glucose challenge have a mean body weight index of 1.04 which is 10% greater than the body weight index (0.95) of the subjects with low plasma insulin levels. This represents a slight (4%) excess above the mean body weight index (1.0) observed in the overall population (Table 4). The effect of a slight body weight excess cannot be ruled out but the association of high plasma insulin and low HDL cholesterol is not related to overt obesity. Similarly when the subjects are stratified according to their HDL cholesterol levels, low HDL cholesterol is associated with high fasting and post-load insulin levels and with a slight body weight excess without overt obesity.

HDL cholesterol is influenced by several factors such as alcohol intake, cigarette smoking and physical activity [35–39]. Lower HDL cholesterol among men with high plasma insulin when compared to men with low plasma insulin, was not related to differences in alcohol consumption, cigarette smoking or physical activity.

Glucose stimulates insulin secretion. The differences in plasma insulin concentrations between the men in the lowest and highest quartiles of plasma insulin could therefore be secondary to different blood glucose levels. This possibility was ruled out as the mean fasting glucose and the mean glucose after the IV load did not differ in subjects with high or low plasma insulin. The mean glucose disappearance rates were within the normal range and did not differ between subjects with high or low endogenous insulin and high or low HDL cholesterol.

There is an interdependence between plasma triglycerides and HDL metabolism [17, 40, 41]. The inverse relationship between HDL cholesterol and VLDL triglyceride levels is well documented [2, 42, 43]. In the present study, the low HDL cholesterol of the subjects with high plasma insulin was not related to differences in VLDL triglyceride levels even though they did tend to have slightly higher VLDL triglyceride levels than men with low plasma insulin.

The increase of HDL triglyceride levels observed among the subjects with high insulin levels after the glucose load indicates that the HDL changes are not merely differences in cholesterol content but represent more profound alterations in the HDL composition. Similar changes have been described in patients

with myocardial infarction [3, 44] and in diabetics [19].

The influence of insulin treatment on HDL has been shown in diabetes [23, 24]. From the present data it appears that even at physiological levels, plasma insulin and HDL cholesterol are closely related. It is indeed striking that factors which are associated with low plasma insulin and increased insulin sensitivity, such as physical activity and leanness [37, 38, 45], tend also to increase HDL cholesterol. On the contrary, factors which decrease HDL cholesterol, such as physical inactivity and obesity, tend to be associated with high plasma insulin [34, 38, 45]. The present data suggest that the low HDL cholesterol in obesity and secondary to physical inactivity could be mediated through the endogenous insulin secretion.

It has been suggested that hyperinsulinism may play a role in the development of atherosclerosis [46–48] and may have a predictive value for the occurrence of coronary heart disease [49]. The association of high plasma insulin and low HDL cholesterol, a known coronary risk factor, needs to be investigated further particularly in relation to tissue and hepatic lipoprotein lipases [17, 40, 50–54].

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Professor D. Pometta
Division de diabétologie
Hôpital Cantonal Universitaire
CH-1211 Geneva 4, Switzerland