

Effects of simvastatin and atorvastatin administration on insulin resistance and respiratory quotient in aged dyslipidemic non-insulin dependent diabetic patients

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Abstract

One hundred and ninety-five aged (mean age: 67 ± 4.8 years), non-insulin dependent diabetic patients underwent a randomised single-blind study for investigating the effect of statin administration on insulin resistance and respiratory quotient. After 4 weeks run-in period, all patients were randomised in three groups: placebo ($n = 67$), simvastatin (10 mg/day) ($n = 61$) and atorvastatin (5 mg/day) ($n = 67$). Each treatment period lasted 8 weeks. At the beginning, after the run-in and at the end of the study, insulin resistance was assessed by homeostasis model assessment (HOMA) index, while respiratory quotient (Rq) was evaluated by indirect calorimetry. Statins versus placebo significantly lowered plasma total, LDL-, HDL-cholesterol and triglyceride concentrations and improved insulin resistance and Rq and metabolic control. Atorvastatin had a greater effect than simvastatin on plasma triglyceride concentration (-26.3 ± 3.1 vs. $-19.7 \pm 2.8\%$, $P < 0.03$), HOMA index (-13.1 ± 0.6 vs. $-9.1 \pm 0.9\%$, $P < 0.05$), Rq (5.9 ± 0.4 vs. $3.1 \pm 0.5\%$, $P < 0.05$) and glycosylated haemoglobin (-11.2 ± 0.3 vs. $-7.1 \pm 0.4\%$, $P < 0.05$). In the whole group of subjects ($n = 195$) and at the end of the study, changes in plasma triglyceride concentrations were significantly correlated with the change in the HOMA index ($r = 0.44$, $P < 0.001$) and age and BMI adjusted-Rq ($r = -0.32$, $P < 0.005$). Multivariate analyses demonstrated that decline in plasma triglyceride concentration was a significant determinant for explaining the effect of statin on insulin resistance and Rq. In conclusion our study demonstrates that statin administration is useful for controlling dyslipidemia in NIDDM patients and for improving the metabolic control. With regard to this latter aim, atorvastatin seems to be more powerful than simvastatin. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Several epidemiological studies have demonstrated that the incidence of coronary heart diseases (CHD) mortality and morbidity in diabetic patients is increased two or three times that in the general population [1]. One of the most important factors contributing to cardiovascular disease in non-insulin dependent diabetes mellitus (NIDDM) patients is the alteration in plasma lipoprotein [2]. Indeed, elevated plasma LDL-

cholesterol and triglyceride concentrations and low plasma HDL-cholesterol levels very frequently occur in NIDDM patients. Advancing age [3] also magnifies such finding. On the other hand, several randomised trials have shown further that significantly lowering LDL-cholesterol and increasing the HDL-cholesterol fraction can produce a regression of the arteriosclerotic lesions [4,5]. Several studies have shown that a modification of dyslipidemia decreases significantly the risk of new CHD events [6,7]. It is noteworthy that plasma triglyceride concentration represents a powerful risk factor for CHD in NIDDM patients [6–9]. Thus, the best treatment of dyslipoproteinemia in NIDDM patients should lower plasma LDL-cholesterol and triglyc-

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eride levels while it should raise plasma HDL-cholesterol concentration. To this regard, 3-hydroxy-3-hydroxymethyl-coenzyme A (HMG-CoA) reductase inhibitors are useful for controlling both hypercholesterolemia and hypertriglyceridemia in NIDDM patients [6,10].

Hyperinsulinemia/insulin resistance is a common feature of NIDDM [11]. The relationship between hyperinsulinemia/insulin resistance with CHD has been reported in several [12–15] but not all studies [16–18]. Among such studies the Insulin Resistance Atherosclerosis Study (IRAS) seems very interesting [19]. In particular, in the IRAS study there was a positive association between insulin resistance and the intimal media thickness of the carotid artery in both Hispanic and non-Hispanic whites. Such a relationship was independent of the traditional cardiovascular disease risk factors, glucose tolerance, and measures of adiposity and fasting insulin levels. Thus, an improvement of insulin action should be a further goal in the therapy of NIDDM patients.

It is widely accepted that elevated plasma triglyceride concentrations may impair insulin action [20,21] through an overactivity of the Randle cycle [22]. Thus, one would expect a lowering in plasma triglyceride concentration can be associated with an improvement of insulin-mediated glucose uptake. Few studies have addressed the potential effects of statins upon insulin actions but results were reached [23–25].

Thus, we aim at investigating the effects of simvastatin and atorvastatin on insulin resistance and substrate oxidation in aged NIDDM patients.

2. Methods

2.1. Patients

One hundred and ninety-five (90F/105M) consecutive NIDDM patients volunteered for our clinical study. All volunteers were outpatients of our Department for diabetics. Eligibility criteria included: (a) age > 60 years; (b) BMI < 27.0 kg/m²; (c) glycosylated haemoglobin (HbA1c) < 8.5%; (d) fasting plasma triglyceride concentrations ranging between 2.5 and 3.2 mmol/l; (e) fasting plasma LDL-cholesterol concentrations ranging between 7.0 and 9.0 mmol/l; (f) no evidence of hypertension or renal, hepatic, endocrine or cancer diseases or severe allergies as determined by medical history, physical examination, and routine laboratory tests. All patients had a stable body weight in the 3 months before the study and were treated by glibenclamide plus metformin and did not take any other drug known to affect plasma glucose and/or lipid concentrations. The purpose, nature and potential risk of the study were explained to all patients and their

voluntary consent was obtained before they were enrolled. The Ethical Committee of our Institution approved the experimental protocol.

2.2. Experimental design

All enrolled patients were treated during 4 weeks run-in period by oral hypoglycaemic agents. A weight-maintaining diet made of 1800 kcal/day, with 50–55% of calories derived from carbohydrate, 20% from proteins and 30% from fat, with < 10% as saturated fatty acids and < 300 mg of cholesterol 24 h⁻¹, was observed throughout the study [26]. Alcohol consumption was permitted up to 1.5 g/day. At the end of the run-in period, all subjects were assigned randomly in single-blind fashion to placebo ($n = 67$), simvastatin (10 mg/day) ($n = 61$) and atorvastatin (5 mg/day) ($n = 67$). Sixty-two smoker patients were distributed equally among the three groups. Drug and placebo treatment periods lasted 8 weeks. At the beginning of the run-in period, at the start of randomisation and at the end of the study, fasting blood samples were drawn for plasma metabolite determination. At the same study times, indirect calorimetry allowed the determination of fasting respiratory quotient (Rq). None of the patients changed their life-style. The level of physical activity was determined according to the method of Haskell [27].

2.3. Analytical methods

Plasma glucose was determined by the glucose oxidase method (Beckman Auto-Analyser, Fullerton, USA). Commercial enzymatic methods were used in the determination of plasma total cholesterol (Moonset Boehringer Mannheim, Milan, Italy) and triglyceride (Peridecrome Boehringer Mannheim, Milan, Italy). Plasma HDL-cholesterol was determined after precipitation of LDL and VLDL lipoprotein with dextran sulfate and magnesium chloride. Plasma LDL-cholesterol was assessed by the Friedwald formula [28]. Glycosylated haemoglobin (HbA1c) was measured by HPLC method ($n.v = 4–6\%$). Specific plasma insulin concentration was measured by commercial double antibody radioimmunoassay (Linco Research, USA; $c.v = 4.5$) in which cross-reactivity with pro-insulin is < 0.2%. Rq was measured by using a computerised open circuit system (Deltatrac, Datex, Milan, Italy) and calculated according to Ferrannini [29].

2.4. Calculations and statistical analysis

Body weight change was calculated having body weight at the end of run-in equal to 100%. Insulin resistance was evaluated by homeostasis model assessment (HOMA) index [30]. Mean arterial blood pressure was calculated as (SBP-DBP)/3 plus DBP. Because

fasting plasma triglyceride and insulin concentrations are extremely skewed, each value was also log-transformed to improve normality for statistical testing and back-transformed for presentation in tables. Changes in plasma lipid and HbA1c concentrations, HOMA index and adjusted-Rq values were calculated having the values at the end of diet therapy equal to 100%.

All values are expressed as means \pm S.D. Comparisons among the different groups were made by analysis of variance (ANOVA). When $P < 0.05$ was found, the Scheffe's test was also applied. Simple linear regression analysis was carried out by standard technique. Analysis of covariance (ANCOVA) allowed adjusting Rq and BMR for age and BMI. Linear multivariate analysis allowed the investigation of the effect of change in plasma triglyceride concentration upon HOMA index and adjusted-Rq values independently of different anthropometric and metabolic covariates. In this latter analysis, drug administration and placebo were used as dummy variables. $P < 0.05$ was chosen as level of significance. All statistical analyses were performed on an IBM PC computer by SigmaStat software analysis.

3. Results

3.1. Clinical characteristics of the patients

All patients were aged (67 ± 4.8 years), slightly overweight (BMI = 26.1 ± 0.8 kg/m²), with a prevalent central body fat distribution (WHR = 0.87 ± 0.03) but not hypertensive (mean arterial blood pressure = 95.3 ± 0.7 mmHg). All patients were affected also by hypertriglyceridemia (2.99 ± 0.22 mmol/l) and hypercholes-

terolemia (LDL-cholesterol = 6.93 ± 0.27 mmol/l) and had low fasting adjusted-Rq (0.78 ± 0.03).

3.2. Effect of diet during the run-in period

In the whole group of patients ($n = 195$) weight-maintaining diet versus baseline values did not significantly affect BMI, fasting plasma glucose, insulin and HDL-cholesterol concentrations (data not shown). In contrast, fasting plasma triglyceride (2.78 ± 0.51 mmol/l, $P < 0.05$), total cholesterol (7.89 ± 0.3 mmol/l, $P < 0.04$) and LDL-cholesterol (6.52 ± 0.38 mmol/l, $P < 0.03$) concentrations and HOMA index (2.7 ± 0.5 , $P < 0.04$) were slightly but significantly lowered by the diet therapy.

Randomisation of the patients in the three groups (Table 1) did not show any significant difference in any variable among the study groups.

3.3. Effect of statins administration (Table 2)

No difference in body weight change and in level of physical activity was found at the end of placebo and statin administration. Statins versus placebo significantly lowered fasting plasma triglyceride, total-, LDL-cholesterol, HbA1c concentrations and HOMA index. In contrast, fasting plasma HDL-cholesterol and adjusted-Rq were improved significantly. Comparing the relative effect of simvastatin and atorvastatin, the latter appeared to be more powerful in decreasing fasting plasma triglyceride concentrations. Both statins were significantly more potent than placebo in affecting HOMA index and Rq (Fig. 1); notwithstanding, atorvastatin displayed a stronger effect than simvastatin on HOMA index and Rq (Fig. 1).

Table 1
Clinical characteristics of the study groups at randomization^a

	Placebo ($n = 67$)	Simvastatin ($n = 61$)	Atorvastatin ($n = 67$)
Age (years)	67.1 ± 2.4	66.1 ± 3.8	68.5 ± 4.6
Gender	29 M/38 F	29 M/32 F	30 M/37 F
BMI (kg/m ²)	25.6 ± 0.8	25.9 ± 0.6	25.8 ± 0.7
WHR	0.85 ± 0.06	0.86 ± 0.03	0.88 ± 0.05
MABP (mmHg)	95.3 ± 0.7	95.1 ± 0.5	95.8 ± 0.8
FP Glucose (mmol/l)	6.4 ± 0.5	6.3 ± 0.2	6.2 ± 0.4
FP Insulin (pmol/l)	70.5 ± 4.3	70.1 ± 3.8	70.8 ± 4.1
HbA1c (%)	7.5 ± 0.5	7.7 ± 0.3	7.6 ± 0.4
FP Triglycerides (mmol/l)	2.79 ± 0.59	2.77 ± 0.51	2.78 ± 0.63
FP Total cholesterol (mmol/l)	7.93 ± 0.51	7.88 ± 0.36	7.91 ± 0.41
FP LDL-cholesterol (mmol/l)	6.56 ± 0.45	6.54 ± 0.41	6.55 ± 0.48
FP HDL-cholesterol (mmol/l)	0.63 ± 0.02	0.61 ± 0.04	0.62 ± 0.03
HOMA index	2.7 ± 0.4	2.7 ± 0.5	2.7 ± 0.6
Adjusted-Rq	0.78 ± 0.05	0.77 ± 0.06	0.78 ± 0.07

^a All results are means \pm S.D. No significant differences between the two experimental conditions were found. BMI, body mass index; WHR, waist/hip ratio; MABP, mean arterial blood pressure; FP, fasting plasma; HbA1c, glycosylated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Rq, respiratory quotient was adjusted for age and BMI.

Table 2
Change (%) in plasma lipids and HbA1c at the end of each treatment period^a

	Placebo	Simvastatin	<i>P</i> ^b	Atorvastatin
FP Triglycerides (mmol/l)	1.6 ± 0.8	−19.7 ± 2.8 *	0.03	−26.3 ± 3.1 *
FP Total cholesterol (mmol/l)	1.8 ± 0.6	−19.1 ± 4.1 *	0.10	−19.4 ± 3.8 *
FP LDL-cholesterol (mmol/l)	2.7 ± 0.5	−19.6 ± 5.5 *	0.13	−20.5 ± 4.1
FP HDL-cholesterol (mmol/l)	1.2 ± 0.3	9.1 ± 3.1 *	0.24	8.7 ± 2.8 *
HbA1c (%)	0.3 ± 0.4	−7.1 ± 0.4 *	0.05	−11.2 ± 0.3 *
Physical activity (METs)	3.2 ± 0.3	3.5 ± 0.2	0.02	3.0 ± 0.2
Body weight change (kg)	−0.7 ± 0.4	−0.6 ± 0.7	0.03	−0.7 ± 0.8

^a All results are means ± S.D. FP, fasting plasma; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin.

^b Differences between simvastatin and atorvastatin are reported as *P*.

* Differences vs. placebo are: *P* < 0.001.

3.4. Analysis in the whole group of patients (*n* = 195)

At baseline, fasting plasma triglyceride concentrations were correlated with BMI ($r = 0.38$, $P < 0.001$), HOMA index ($r = 0.41$, $P < 0.001$) and adjusted-Rq ($r = -0.36$, $P < 0.001$). In the whole group of subjects ($n = 195$) and at the end of the study, changes in plasma triglyceride concentrations were significantly correlated with the change in HOMA index ($r = 0.44$, $P < 0.001$) and adjusted-Rq ($r = -0.32$, $P < 0.005$). At the same study time, a multivariate analysis ($n = 195$) allowed the investigation of the relative contribution of the different covariates to the change in HOMA index (Table 3). A model made by changes in plasma triglyceride and LDL-concentrations, simvastatin administration (yes/no), atorvastatin administration (yes/no) and placebo (yes/no) was tested. In such model only changes in plasma triglyceride concentrations were significantly and independently associated ($t = 6.12$, $P < 0.006$) with the changes in the HOMA index. Furthermore, the main determinants of the change in Rq were investigated (Table 3). Thus, a model made by changes in plasma triglyceride concentrations, change in the HOMA index, simvastatin administration (yes/no), atorvastatin administration (yes/no) and placebo (yes/no) was used. Only changes in plasma triglyceride concentrations ($t = -5.88$, $P < 0.006$) and in the HOMA index ($t = -3.18$, $P < 0.01$) were significantly and independently associated with the changes in Rq.

4. Discussion

Our study demonstrates that: (a) both statins were equally effective on lowering plasma total and LDL-cholesterol levels and on raising plasma HDL-cholesterol levels while atorvastatin had a stronger effect than simvastatin on plasma triglyceride concentrations; (b) both statins had favourable effects upon insulin resistance and substrate oxidation; nevertheless, atorvas-

tatin administration was associated with a marked reduction in insulin resistance and improvement in substrate oxidation and glucose metabolic control than simvastatin did; (c) improvement in insulin action and substrate oxidation were significantly correlated with the lowering in plasma triglyceride concentration.

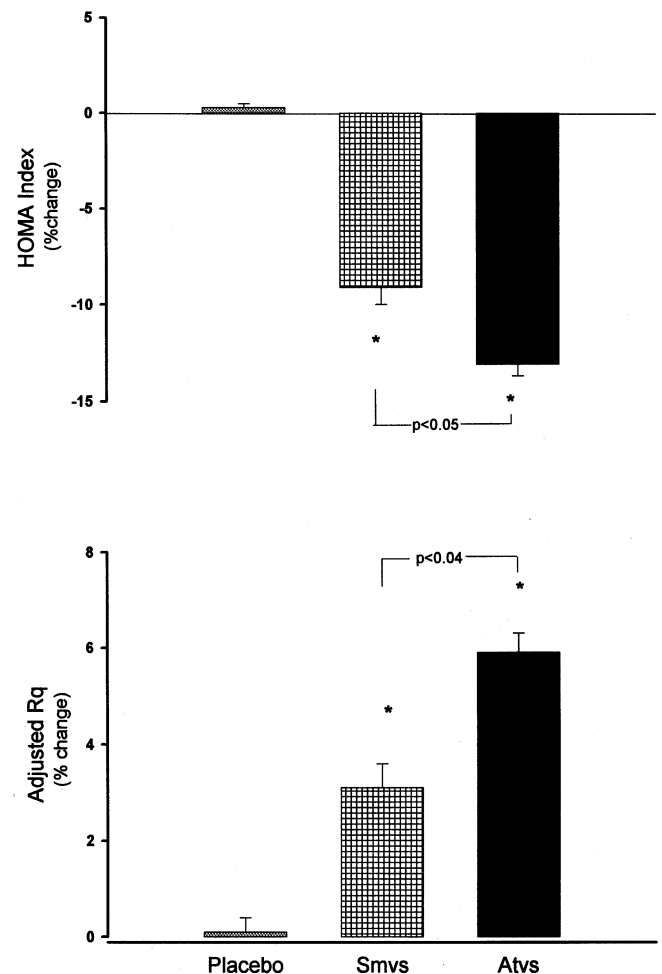


Fig. 1. Changes in the HOMA index (top) and adjusted-respiratory quotient (Rq) (bottom) after 8-weeks placebo, simvastatin (10 mg/day) and atorvastatin (5 mg/day) administration. Difference vs. placebo are: * $P < 0.005$. Rq was adjusted for age and BMI.

Table 3
Linear multiple regression analyses with change in HOMA index and change in Rq as dependent variables

Variable	<i>t</i>	<i>P</i>
<i>Change in HOMA index</i>		
Triglycerides	6.12	0.006
LDL-Cholesterol	0.08	0.32
Simvastatin (yes/no)	0.41	0.15
Atorvastatin (yes/no)	0.93	0.09
Placebo (yes/no)	0.18	0.96
<i>Change in Rq</i>		
Change in Triglycerides	−5.80	0.006
Change in HOMA index	−3.18	0.01
Simvastatin (yes/no)	0.48	0.18
Atorvastatin (yes/no)	0.99	0.11
Placebo (yes/no)	0.21	0.97

A finding of our study was the evidence that atorvastatin was more potent than simvastatin in lowering plasma triglyceride concentration. Such result is in agreement with a previous finding in type 2 diabetic patients having clinical characteristics not very different from ours [6]. Why atorvastatin is more potent than simvastatin on lowering plasma triglyceride concentration is not understood completely. One could argue that an unbalanced dose comparison between atorvastatin and simvastatin could provide a reason for our data. However, such a possibility seems unlikely. In fact, atorvastatin has been shown to be twice as potent as simvastatin and thus, in our experimental design, a dose of 5 mg of atorvastatin was compared with 10 mg of simvastatin [6]. Furthermore, the triglyceride/LDL cholesterol ratio, an index used widely to standardise assessment across drugs, doses and basal lipid on comparing statins [31] was 1.0 with simvastatin and 0.9 with atorvastatin. Thus, other mechanism/s than the dose should be taken into account. Briefly, it has been hypothesised that atorvastatin might affect plasma triglyceride concentration either through an increased removal of triglyceride rich-lipoproteins or a decreased hepatic secretion of apolipoprotein B particles such as VLDL in those subjects with excessive production rates or both [31]. Alternatively, atorvastatin has been shown to result in more sustained plasma concentration than simvastatin [32,33], thus have a more sustained effect on plasma triglycerides that have a very rapid rate of turnover.

A greater lowering effect of atorvastatin upon plasma triglyceride concentration might provide an explanation for the reduction in insulin resistance and improvement in metabolic control observed in our patients. The relationship occurring between insulin resistance and dyslipidemia is supported by several epidemiological data. In particular, Laakso et al. [34] showed the relationship between insulin resistance and lipoproteins in

individuals with varying degrees of glucose intolerance and revealed lower concentration of HDL and high total VLDL-triglyceride among those who were insulin resistant. Population based studies have almost universally revealed links among insulin, triglyceride and HDL. The CARDIA Study examined insulin and lipid in black and in white young adults [35]. In this study positive relationship between plasma insulin and triglyceride concentration was found among both racial groups, a result independent of age, gender and BMI. In 1992, the French Telecom Study, which compared characteristics of the insulin resistance syndrome in Caribbeans and Caucasians, found that higher insulin concentrations in the Caribbean group were associated with higher levels of triglyceride after adjustment for age and BMI [36]. Finally, similar results were confirmed in the Strong Heart Study [37].

Whether insulin resistance is the cause or the effect of elevated plasma triglyceride concentration in type 2 diabetic patients is still an unsolved question. Indeed, it is widely accepted that elevated plasma triglyceride concentration and insulin resistance may work in a vicious circle. In fact, insulin resistance allowed an increased production and flow of free fatty acids from the abdominal viscera to the liver [38], where these fatty acids accelerate triglyceride production. Such negative effect of insulin resistance is magnified by the occurrence of hyperglycaemia, which also increases VLDL production by the liver [39]. On the other hand, elevated plasma triglyceride concentration is responsible for an overactivity of the Randle cycle due to a prevalent lipid oxidation. The latter phenomenon, in turn, has been shown to impair insulin-mediated glucose metabolism in both oxidative and non-oxidative components [22]. In our study, statins administration was associated with an improvement of insulin resistance and Rq, and decline in plasma triglyceride concentration; such relationship was found in the multivariate analyses showing changes in plasma triglyceride concentrations to be significantly associated with the change in the HOMA index and Rq. Thus, lower plasma triglyceride availability might be responsible for a shift from lipid to glucose as the main intracellular substrate source. From the clinical point of view, this more favourable glucose handling was associated with a better metabolic control which, on the other hand, was unaffected by changes in dosage of hypoglycaemic agents or in BMI.

The effects of statins administration upon insulin action and metabolic control in NIDDM patients have been the subject of previous investigations [23–25]; unfortunately, a great discrepancy among the results was found. Our group used the euglycemic hyperinsulinemic glucose clamp for demonstrating that simvastatin administration was associated with a significant decline in plasma triglyceride and improvement in in-

sulin-mediated glucose uptake measured in aged NIDDM patients [23]. Farrer et al. [24] confirmed that simvastatin lowers plasma triglyceride concentration but they did not observe any benefit upon fasting plasma glucose, insulin and HbA1 concentration in NIDDM patients. However, the small number of patients treated ($n=28$), the large age range (25–70 years), a different time duration of the study and the lack of direct (euglycemic hyperinsulinemic glucose clamp) or indirect (HOMA index) measurements of insulin action might explain the discrepancy with our data. Ohrvall et al. [25] compared also the efficacy of gemfibrozil with simvastatin in NIDDM patients. The unexpected findings were the lack of any effect of simvastatin on plasma triglyceride concentration and a worsening of insulin action as measured by the intravenous glucose tolerance test. Nevertheless, almost 50% of such patients were hypertensives treated by B-blockers, calcium blockers, angiotensin-converting enzymes (alone or in combination), and thus affected by a type of insulin resistance different from that in NIDDM patients and therefore not responsive to statins administration.

In conclusion, our study demonstrates that statins administration is useful for controlling dyslipidemia in NIDDM patients and for improving the metabolic control. Atorvastatin seems to be more potent than simvastatin; nevertheless, greater and longer studies than ours are needed to better highlight the metabolic potency and efficacy of these two statins in NIDDM patients.

References

- [1] Dean JD, Durrington PN. Treatment of dyslipoproteinaemia in diabetes mellitus. *Diabet Med* 1996;13:297–312.
- [2] Howard BV, Howard WJ. Dyslipidemia in non-insulin dependent diabetes mellitus. *Endocr Rev* 1994;15:263–74.
- [3] Cefalu WT, Werbel S, Bell-Farrow AD, Terry JG, Wang ZQ, Opara EC, Morgan T, Hinson WH, Crouse JR. Insulin resistance and fat patterning with aging: relationship to metabolic risk factors for cardiovascular disease. *Metabolism* 1998;47:401–8.
- [4] Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, Zhao XQ, Bisson BD, Fitzpatrick VF, Dodge HT. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;323:1289–98.
- [5] Kane JP, Mallory MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ. Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. *J Am Med Assoc* 1990;264:3007–12.
- [6] Haffner SM. Management of dyslipidemia in adults with diabetes. *Diabetes Care* 1998;21:160–78.
- [7] Gotto AM Jr, Grundy SM. Lowering LDL cholesterol: questions from recent meta-analyses and subset analyses of clinical trial DataIssues from the Interdisciplinary Council on Reducing the Risk for Coronary Heart Disease, Ninth Council Meeting. *Circulation* 1999;99(8):E1–7.
- [8] Fontbonne A, Eschwege E, Cambien F, Richard JL, Ducimetre P, Thibault N, Warnet JM, Claude JR, Rosselin GE. Hypertriglyceridemia as a risk factor for coronary heart disease mortality in subjects with impaired glucose tolerance on diabetes: results from the 11-year follow-up of the Paris Prospective Study. *Diabetologia* 1989;32:300–4.
- [9] Laakso M, Lehto S, Penttila I, Pyorala K. Lipids and lipoprotein predicting coronary heart disease mortality and morbidity in patients with non-insulin dependent diabetes. *Circulation* 1993;88:1421–30.
- [10] Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins. Implications for cardiovascular event reduction. *J Am Med Assoc* 1998;279:1643–50.
- [11] Ferrannini E. Insulin resistance vs. insulin deficiency in non-insulin dependent diabetes mellitus: problems and prospects. *Endocr Rev* 1998;19:477–90.
- [12] Eschwege E, Richard JL, Thibault N, Ducimetre P, Warnet JM, Claude JR, Rosselin GE. Coronary heart mortality in relation to diabetes, blood glucose and plasma insulin levels: the Paris Prospective Study, 10 years later. *Horm Metab Res* 1985;15:41–6.
- [13] Després JP, Lamarche B, Mauriege P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ. Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med* 1996;334:952–7.
- [14] Welborn TA, Weane K. Coronary heart disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentrations. *Diabetes Care* 1974;2:154–60.
- [15] Pyorala K, Savolainen E, Kaukola S, Haapakoski J. Plasma insulin as coronary heart diseases risk factor: relationship to other risk factors and predictive during 9 1/2 year follow-up of the Helsinki Policeman Study population. *Acta Med Scand* 1985;701:38–52.
- [16] Orchard TJ, Eichner J, Kuller LH, Becker DJ, McCallum LM, Granditis GA. Insulin a predictor of coronary heart disease: interaction with apolipoprotein E phenotype: a report from the Multiple Risk Factor Intervention Trial. *Ann Epidemiol* 1994;4:40–5.
- [17] Ferrara A, Barrett-Connor E, Edelstein SL. Hyperinsulinemia does not increase the risk of fatal cardiovascular disease in elderly men with and without diabetes: the Rancho Bernardo Study. *Am J Epidemiol* 1992;140:857–69.
- [18] Welin L, Eriksson H, Larsson B, Ohlson LO, Svardsudd K, Tibblin G. Hyperinsulinemia is not a major coronary risk factor in elderly men: the study of men born in 1913. *Diabetologia* 1992;35:766–70.
- [19] Howard G, O'Leary DH, Zaccaro D, Haffner SM, Rewers M, Hamman R, Selby JV, Saad MF, Savage P, Bergman R. Insulin sensitivity and atherosclerosis. *Circulation* 1996;93:1809–17.
- [20] Rigalleau V, Beylot M, Pachaiaud C, Guillot C, Deleris G, Gin H. Mechanisms of glucose intolerance during triglyceride infusion. *Am J Physiol* 1998;275(4, Pt. 1):E641–8.
- [21] Mingrone G, Henriksen FL, Greco AV, Krogh LN, Capristo E, Gastaldelli A, Castagneto M, Ferrannini E, Gasparrini G, Beck-Nielsen H. Triglyceride-induced diabetes associated with familial lipoprotein lipase deficiency. *Diabetes* 1999;48(6):1258–63.
- [22] Randle PJ, Garland PB, Hales CN, Newsholme FA. The glucose fatty acid cycle. Its role in insulin sensitivity and the metabolic disturbance of diabetes mellitus. *Lancet* 1963;1:785–9.
- [23] Paolisso G, Sgambato S, De Riu S, Marrazzo G, D'Onofrio F. Simvastatin reduces plasma lipid levels and improves insulin action in elderly non-insulin dependent diabetics. *Eur J Clin Pharmacol* 1991;40:27–31.
- [24] Farrer M, Winocur PH, Evans K, Neil HAW, Laker MF, Kevesten P, Alberti KGMM. Simvastatin in non-insulin dependent diabetes mellitus: effect on serum lipid, lipoproteins and haemostatic measures. *Diabetes Res Clin Pract* 1994;23:111–9.

- [25] Orhvald M, Lithell H, Johansson J, Vessby B. A comparison between the effects of gemfibrozil and simvastatin on insulin sensitivity in patients with non-insulin dependent diabetes mellitus and hypolipoproteinemia. *Metabolism* 1995;44:212–7.
- [26] British Diabetic Ass. Nutrition Subcommittee. Dietary recommendations for people with diabetes. An update for the 1990s. *Diabet. Med.* 1992;9:189–202.
- [27] Haskell WL. Design and implementation of cardiac conditioning progress. In: Wenger NK, Hellerstein H, editors. *Rehabilitation of the Coronary Patient*. New York: Wiley, 1978:203–41.
- [28] Friedwald WT, Levy R, Fredrickson DS. Estimation of serum low density lipoprotein without the use of a preparative ultracentrifuge. *Clin Chem* 1978;18:499–502.
- [29] Ferrannini E. The theoretical basis of indirect calorimetry: a review. *Metabolism* 1988;37:287–301.
- [30] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and B-cell function from plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–9.
- [31] Stein EA, Lane M, Laskarzewski P. Comparison of statins in hypertriglyceridemia. *Am J Cardiol* 1998;81(4A):66B–9B.
- [32] Aguilar-Salinas CA, Barrett H, Schonfeld G. Metabolic modes of action of the statins in the hyperlipoproteinemias. *Atherosclerosis* 1998;141(2):203–7.
- [33] Crouse JR, Frohlich J, Ose L, Mercuri M, Tobert JA. Effect of high doses of simvastatin and atorvastatin on high-density lipoprotein cholesterol and apolipoprotein A-I. *Am J Cardiol* 1999;83(10):1476–1477, A7.
- [34] Laakso M, Sarlund H, Mykkannen L. Insulin resistance is associated with lipid and lipoprotein abnormalities in subjects with varying degree of glucose tolerance. *Arteriosclerosis* 1990;10:223–31.
- [35] Manolio TA, Savage PJ, Burke GL, Liu K, Wagneknecht LE, Sidney S, Jacobs DR, Roseman JM, Donahue RP, Oberman A. Association of fasting insulin with blood pressure and lipid in young adults. *Arteriosclerosis* 1990;10:430–6.
- [36] Fontbonne A, papoz L, Eschwege E, Roger M, Saint- Paul M, Simon D. Features of insulin-resistance syndrome in men from the French Caribbean island. *Diabetes* 1992;41:1385–9.
- [37] Howard BV, Welty TK, Fabsitz RR, Cowan LD, Oopik A, Le NA, Yeh JL, Lee ET. Risk factors for coronary heart disease in diabetic and non diabetic native Americans. *Diabetes* 1992;14:4–11.
- [38] Fujioka S, Matsuzawa Y, Tokunage K, Tarui S. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism* 1987;36:54–9.
- [39] Anderson AJ, Sobocinski KA, Freedman DS, Barboriak JJ, Rimm AA, Gruschow HW. Body fat distribution plasma lipids and lipoproteins. *Arteriosclerosis* 1988;8:88–94.