

# The effect of glycemic control in type 2 diabetic patients with diabetes-related dyslipidemia

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## ABSTRACT

**Objective:** The study was planned to investigate whether the serum lipid profile in type 2 diabetes mellitus was different between groups of patients classified as having good, satisfactory or poor glycemic controls, depending on their serum fructosamine levels.

**Methods:** The study was carried out in the Department of Laboratory, Dammam College for Health Sciences, Dammam, Kingdom of Saudi Arabia between February 2003 to June 2003. Clinical laboratory data from diagnosed type 2 diabetic patients were used in the study. One hundred and nineteen patient's data were randomly selected, and according to their serum fructosamine levels, the patients were divided into 3 groups: 29 patients classified as patients with good glycemic control (GGC) with serum fructosamine level  $<250 \mu\text{mol/L}$ , 44 patients classified as satisfactory glycemic control (SGC) with serum fructosamine level ranging between  $250\text{--}355 \mu\text{mol/L}$  and 46 patients classified as poor glycemic control (PGC) with serum fructosamine  $>355 \mu\text{mol/L}$ . The fasting serum glucose and various lipids and lipoprotein concentrations of each group were analyzed by one way analysis of variance and regression analysis.

**Results:** In the PGC group, the serum total cholesterol

( $6.11 \pm 1.56 \text{ mmol/L}$ ), triglyceride ( $2.13 \pm 0.71 \text{ mmol/L}$ ) and very low density lipoprotein-cholesterol ( $1.09 \pm 0.40 \text{ mmol/L}$ ) concentrations were significantly higher than that of the SGC ( $5.59 \pm 0.89$ ,  $1.59 \pm 0.38$  and  $0.86 \pm 0.28 \text{ mmol/L}$ ), and the GGC ( $5.11 \pm 1.06$ ,  $1.25 \pm 0.32$  and  $0.78 \pm 0.29 \text{ mmol/L}$ ), whereas, those of the SGC were slightly raised, but not statistically significant, compared to the GGC. The high density lipoprotein cholesterol was significantly lower, and the low density lipoprotein cholesterol was elevated in both satisfactory and poorly controlled groups compared to good control group. Significant correlations were evident between the serum fructosamine and glucose concentrations ( $r=0.79$ ,  $p<0.0001$ ), and between them as independent parameters and the serum lipid concentrations.

**Conclusion:** The glycemic control in type 2 diabetes significantly improves diabetic related dyslipidemia, and would be expected to reduce the risk of atherosclerosis. It is also worth mentioning that the serum fructosamine measure gives a good index for the glycemic control, and its value can reflect the profile of serum lipids.

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Cardiovascular disease is the leading cause of death in patients with non insulin-dependent DM.<sup>1</sup> Abnormal lipid metabolism, presented as hypercholesterolemia and hypertriglyceridemia, is a common finding among the diabetics,<sup>2</sup> and it is considered a risk factor for premature atherosclerosis.<sup>3</sup> Increased oxidizability of low density lipoprotein (LDL) is believed to be partly

responsible for the diabetic-related dyslipidemia.<sup>4</sup> In the uncontrolled diabetes, glycation and oxidative modification of the lipoproteins enhance the uptake of these lipids by macrophages initiating the early stages of atherosclerosis.<sup>5</sup> The present study was carried out to investigate the effect of medium term glycemic control in patients with type 2 diabetes mellitus (DM) on the occurrence and progression of

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dyslipidemia, and to correlate between the glycemic indices and the serum lipid profile. Since serum fructosamine level is believed to be a reliable index for medium-term glycemic control,<sup>6</sup> the study groups were allocated according to their serum fructosamine levels.

**Methods.** The study was conducted on clinical data of patients with type 2 DM who were visiting the Diabetic and Endocrinology Out-Patient Unit of Dammam Central Hospital, Dammam, Kingdom of Saudi Arabia. The fasting blood samples of the patients were analyzed in the clinical laboratory of the hospital. The patient's clinical data entered in the record book of the laboratory for the period from February 2003 to May 2003 was used in this study. Clinical data of 119 patients with normal kidney function, and liver function were randomly selected for the study. Depending on their serum fructosamine levels, the patients were classified into Group A - 29 patients (10 male and 19 female) classified as good glycemic control (GGC) subjects with serum fructosamine <250 µmol/L. Group B - patients with satisfactory glycemic control (SGC) group consist of 44 patients (14 male and 30 female) with fasting serum fructosamine range of 250- 355 µmol/L, and Group C - patients with poor glycemic control (PGC) group consist of 46 patients (20 male and 26 female) with serum fructosamine level >355 µmol/L. All patients had an age range of 42-67 years (mean age was 51 ± 3.20 years). The patients had not taken insulin or other medication for a minimum of 10 hours prior to the blood sample collection.

**Biochemical assays.** The serum concentrations of glucose, fructosamine, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, total cholesterol, triglyceride, high density lipoprotein (HDL) and LDL cholesterol were assayed by the automated spectrophotometer, Hitachi-717, utilizing commercial kits supplied by Roche Diagnostic, United Kingdom. The very low density lipoprotein (VLDL)-cholesterol was calculated by subtraction of LDL-cholesterol + HDL cholesterol fractions from total cholesterol, and the ratio of HDL-cholesterol/ total-cholesterol was calculated by dividing the 2 means of each group. Fructosamine index was calculated by dividing fructosamine (mmol/L)/glucose (mmol/L).

**Statistical analysis.** The presented data are mean ± SD. The significance of differences between the means was computed by one way analysis of variance, followed by Multiple Comparison Analysis. Spearman's regression analysis was used to study the significance of correlation between serum glucose versus fructosamine, or between glucose and fructosamine as independent parameters and the individual serum lipids as dependent parameters. *P* value less than 0.05 was considered significant.

**Results.** The GGC group had a fasting serum fructosamine levels ranging between 179.93-233.43 µmol/L, and glucose levels ranging between 3.61-6.11 mmol/L, whereas, the SGC group had a serum fructosamine range of 259.50-339.86 µmol/L and glucose range of 6.66-10.10 mmol/L, with mean values of 277.02 ± 44.56 µmol/L and 9.00 ± 1.57 mmol/L. The PGC group, on the other hand, had a fasting serum fructosamine range of 359.85-649.93 µmol/L and glucose range of 11.11-24.38 mmol/L. As shown in **Table 1**, the SGC group had their mean serum glucose concentration significantly (*p*<0.01) higher than that of the GGC by 56.2%, and the Fructosamine by 16.5% (*p*<0.05). The PGC group had their serum glucose level higher than that of the GGC subjects by 2.3-fold and the fructosamine level higher by 80.2%. In contrast, the fructosamine index showed a concomitant reduction with increase in glucose and fructosamine concentrations. In the SGC group it was reduced by 25% compared to the GGC, whereas, in the PGC group the reduction was by 50% compared to the GGC, and by 33.3% compared to the SGC group. A strong correlation was evident between the serum glucose and the fructosamine level (*r*=0.79, *p*<0.0001). The serum total cholesterol in the SGC group showed a trend of increase by 9.5% compared to GGC, but not statistically significant. However, in the PGC group the cholesterol level was significantly (*p*<0.01) increased by 19.5% compared to the GGC, and by 9.1% (*p*<0.05) compared to the SGC group (**Table 2**). A significant correlation was evident between the serum glucose and the cholesterol concentration (*r*=0.47, *p*<0.001), and between the fructosamine and cholesterol levels (*r*=0.47, *p*<0.001). Similarly, the serum triglyceride exhibited a significant (*p*<0.001) increase in the PGC group which amounted to 70.4% compared to the GGC group and by 33.9% (*p*<0.05) compared to the SGC group, whereas, the SGC group showed a trend of increase by 27.3% which was not statistically significant. A significant correlation was observed between the serum glucose concentration and the serum triglyceride (*r*=0.43, *p*<0.01), and between the fructosamine and the triglyceride (*r*=0.34, *p*<0.05). The triglyceride/cholesterol % showed a trend of increase with increase in the serum glucose and fructosamine concentrations. In the SGC group, the increase was by 16.2% and by 42.5% in the PGC group compared to the GGC. **Table 3** summarizes the lipoprotein profile in the study groups. The VLDL-cholesterol fraction was raised in the PGC group by 38.8% (*p*<0.05) compared to the GGC, and by 27.3% (not statistically significant) compared to the SGC group. Similarly, the LDL-cholesterol was significantly (*p*<0.01) increased by 20.8% in the SGC group and by 33% (*p*<0.001) in the PGC group compared to GGC. In contrast, the HDL-cholesterol in the SGC group

Table 1 - Fasting serum glucose and fructosamine concentrations and fructosamine index in type 2 diabetic patients with good glycemic control (GGC) satisfactory glycemic control (SGC) and poor glycemic control (PGC).

Parameter	GGC (n=29)	SGC (n=44)	PGC (n=46)
Serum glucose (mmol/L)	5.76±0.56	9.00±1.57 <sup>§,*</sup>	19.02±4.58 <sup>§,†,II,‡</sup>
Serum fructosamine (µmol/L)	237.63±40.69	277.02±44.56 <sup>§,*</sup>	428.39±85.51 <sup>§,†,II,‡</sup>
Fructosamine index <sup>**</sup>	0.04	0.03	0.02

Presented data are mean ± SD. \**p*<0.05, †*p*<0.01, ‡*p*<0.001, §significantly different from GGC, IIsignificantly different from SGC, \*\*moles of fructosamine per mole of glucose

Table 2 - Fasting serum total cholesterol and triglyceride concentrations and the triglyceride/cholesterol percentage in type 2 diabetic patients with good glycemic control (GGC), satisfactory glycemic control (SGC) or poor glycemic control (PGC).

Parameter	GGC (n=29)	SGC (n=44)	PGC (n=46)
Cholesterol (mmol/L)	5.11±1.06	5.59±0.89	6.11±1.56 <sup>§II*</sup>
Triglyceride (mmol/L)	1.25±0.32	1.59±0.38	2.13±0.71 <sup>§II*</sup>
Triglyceride/cholesterol percentage	24.46	28.44	34.86

Presented data are mean ± SD. \**p*<0.05, †*p*<0.01, ‡*p*<0.001, §significantly different from GGC, IIsignificantly different from SGC

Table 3 - Serum lipoprotein profile in type 2 diabetic patients with good glycemic control (GGC), satisfactory glycemic control (SGC) or poor glycemic control (PGC).

Parameter	GGC (n=29)	SGC (n=44)	PGC (n=46)
High density lipoprotein-cholesterol (mmol/L)	1.35±0.53	1.13±0.20 <sup>§*</sup>	1.08±0.18 <sup>§*</sup>
Very low density lipoprotein-cholesterol (mmol/L)	0.78±0.29	0.86±0.28	1.09±0.40 <sup>§*</sup>
Low density lipoprotein-cholesterol (mmol/L)	3.01±0.59	3.62±0.55 <sup>§†</sup>	4.01±0.64 <sup>§‡</sup>
High density lipoprotein/total-cholesterol ratio	0.26	0.2	0.17

presented data are mean ± SD. \**p*<0.05, †*p*<0.01, ‡*p*<0.001, §significantly different from GGC

showed a significant (*p*<0.05) reduction (from 1.35 ± 0.53 to 1.13 ± 0.20 mmol/L), and a 20% reduction (*p*<0.05) in the PGC group (from 1.35 ± 0.53 to 1.08 ± 0.18 mmol/L), compared to the GGC group (Normal values 0.80-1.94 mmol/L). The HDL cholesterol/total cholesterol ratio exhibited a reduction by 23% in the SGC group and by 34.6% in the PGC group. A significant positive correlation existed between the fructosamine index and the HDL/total cholesterol ratio (*r*=0.67, *p*<0.001).

**Discussion.** Patients with type 2 DM are at increased risk of coronary heart diseases. A study by Rahman<sup>7</sup> revealed a high prevalence of metabolic risk factors for the cardiovascular diseases within the Saudi population. Among the main risk factors was the DM especially prevalent among females. Harris<sup>8</sup> reported that hypercholesterolemia was present in 70% of the diagnosed diabetic patients in the United States of America, and 95% of these patients had evidence of coronary heart disease. The fasting serum fructosamine concentration of 277µmol/L for a glucose level of 9mmol/L observed in the present study was apparently lower than some of the reported values in literature. Fructosamine value of 3280±160 µmol/L has been found in diabetic patients with glucose level of 9.50mmol/L,<sup>9</sup> and a value of 2040 µmol/L was reported in gestational diabetes.<sup>10</sup> Nevertheless, our values were in line with the fructosamine value of 320µmol/L reported in Indonesian diabetic patients.<sup>11</sup> This variance in the fructosamine values probably reflects the environmental variation and the dietary style in these populations. This requires cautiousness when comparing between results from different populations. However, results of the fructosamine index in the present study showed that the rate of increase in the glycosylation of proteins falls with increase in the serum glucose concentration. This probably indicates a saturation stage of protein glycosylation (or fructosamine formation) attained as a result of persistent hyperglycemia. Uncontrolled DM is known to be associated with secondary dyslipidemia.<sup>12</sup> The present results have shown that the groups with good and satisfactory glycemic controls did not develop hyperlipidemia, considering the reported upper limits of the serum lipids.<sup>13</sup> However, the patients with poor glycemic control developed significant hypercholesterolemia and hypertriglyceridemia. Our results indicated that the hypercholesterolemia was associated with the significantly elevated VLDL cholesterol and LDL cholesterol fractions with diminished HDL cholesterol. This was in congruence with several reports.<sup>12,14</sup> Grundy et al<sup>15</sup> have demonstrated overproduction of apoprotein B in type 2 DM,

leading to increased hepatic synthesis of VLDL. As shown in the present study, the patients with controlled blood glucose level exhibited elevated LDL with sub-normal VLDL cholesterol level, whereas, the patients with poorly controlled hyperglycemia had both lipoprotein fractions significantly elevated. This probably indicates that under satisfactory glycemic control the process of VLDL clearance was still functioning at a normal rate. It has been reported that in uncontrolled diabetes the activity of lipoprotein lipase, the enzyme responsible for the clearance of VLDL in circulation, was diminished due to the insulin resistance.<sup>12</sup> The persistent hyperglycemia and the increased concentration of ketone bodies in circulation in uncontrolled DM are known to modify the LDL particles. An atherogenic type of LDL (small dense LDL) is known to be formed at an increased rate in the diabetics by a non-enzymatic glycation of its apoprotein B.<sup>16</sup> Furthermore, due to the increased free radical production in uncontrolled diabetes, the LDL particles are subject to oxidation.<sup>17</sup> The modified LDL particles (by oxidation and glycation) are poorly recognized by the receptors and their binding and uptake is diminished leaving more LDL in circulation. Part of the modified LDL is trapped in the extracellular matrix of the endothelial tissue, which is known to be cytotoxic and believed to be a major factor in the process of atherosclerosis.<sup>18</sup> The small dense LDL formed in uncontrolled diabetes was found more susceptible to oxidation by free radicals than the native lipoprotein, and was poorly protected by antioxidants from the free radical challenge.<sup>19-21</sup> Hyper triglyceridemia was found to favor formation of the atherogenic dense LDL,<sup>22</sup> and the dense glycosylated LDL isolated from diabetic patients was shown to be enriched in triglycerides than the non-glycosylated LDL from the same patients.<sup>23</sup> The present results have shown that both hyperglycemia and hyper triglyceridemia were present in the PGC group; a condition which would enhance production of the modified LDL. This was supported by the significantly elevated LDL in this group which amounted to 65% of the total cholesterol. Although the LDL content in the individuals with satisfactorily controlled glycemia was also high, but the triglyceride content of these lipoproteins was probably lower in the controlled group. This was evidenced by the fact that the total triglyceride/total cholesterol percentage in the SGC group was 28.4% whereas, in the PGC group it was 34.8%, a condition which would favor the production of more atherogenic LDL in the PGC group. The relative proportion of cholesterol ester transferred from HDL to VLDL<sup>1</sup> in type 2 diabetes was found to be

increased progressively with increase in the plasma triglyceride level and the dense LDL was shown to acquire a large proportion of the cholesterol ester transferred from HDL to LDL.<sup>22</sup> This probably explains the significantly diminished HDL cholesterol in the uncontrolled-diabetic group with concomitant increase in the total LDL and VLDL cholesterol fractions. All these conditions seem to have exacerbated the diabetic-related dyslipidemia rendering a more atherogenic condition in patients with poorly controlled persistent hyperglycemia.

In conclusion, the present results have highlighted the deleterious effects of the persistent hyperglycemia in diabetic patients with poor glycemic control, and the primer role played by the glycosylated LDL in initiation and progression of the dyslipidemia.

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