ORIGINAL ARTICLE

# SIGNIFICANCE OF GLYCAEMIC CONTROL IN TYPE 1 DIABETES

**Maryam Wahid, Abdul Khaliq Naveed***

**Department of Biochemistry, Foundation University Medical College, Islamabad,**
***Department of Biochemistry & Molecular Biology, Army Medical College, Rawalpindi, Pakistan**

**Background:** Diabetes mellitus is accompanied with drastic hormonal and metabolic alterations. In uncontrolled diabetes, these disturbances worsen the condition leading to development of life threatening complications. Present study was planned to compare hormonal and metabolic disturbances in controlled and uncontrolled type 1 diabetes (T1D). **Methods:** This retrospective, analytical case control study was carried out from Jan 2004 to July 2007. Sample size was 60, divided into 3 groups: Non-diabetic control (group A), controlled T1D (group B) and uncontrolled T1D (group C). **Results:** Uncontrolled type 1 diabetics when compared with control group, presented with significant hyperglycaemia ($p<0.001$), hypoinsulinemia ($p<0.001$), hyperglucagonemia ($p<0.01$), raised BMI ($p<0.05$), hyponatremia ($p<0.01$), hyperkalemia ($p<0.01$), acidemia ($p<0.05$), high arterial $Pco_2$ ($p<0.05$), low plasma $HCO_3^-$ ($p<0.05$), raised plasma triglyceride, LDL Cholesterol and total cholesterol level ($p<0.01$) but low HDL cholesterol ($p<0.05$). On similar comparison controlled type 1 diabetics showed significant hyperglycaemia ($p<0.001$) and hypoinsulinemia ($p<0.05$). **Conclusion:** Regular assessment, monitoring and control of T1D has positive impact in preventing development of diabetic dyslipidemia and other hormonal and metabolic derangements which, if left uncontrolled can lead to life threatening diabetic complications.

**Keywords:** Type 1 diabetes, Diabetic Ketoacidosis, Dyslipidemia, Hypoinsulinemia, Hyperglycaemia, hyperglucagonemia

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## INTRODUCTION

Type 1 diabetes (T1D) is a chronic disorder resulting due to progressive autoimmune destruction of the beta pancreatic cells of the islets of Langerhans leading to inadequate insulin production and subsequent hyperglycaemia. Hyperglycaemia is the most prominent feature of diabetes mellitus (DM). Persistent uncontrolled hyperglycaemia leads to life crippling complications like diabetic ketoacidosis, retinopathies, renal dysfunction, atherosclerosis and stroke.[1] These two main gluco-regulatory hormones regulate glucose metabolism. Insulin controls postprandial rise in plasma glucose level by increasing its uptake by peripheral tissues specially muscles. Insulin also enhances hepatic glycogenesis and exerts an inhibitory effect on pancreatic glucagon release.[2] Hyperglycaemic hormone, glucagon acts via receptors on adipocytes. It enhances lipolysis and release of non-esterified free fatty acid into plasma. Uncontrolled T1D is usually accompanied with hypoinsulinemia and relative hyperglucagonemia which play a significant role in worsening the disease outcomes.[3]

According to National Cholesterol Education Program (NCEP) guidelines dyslipidemia is defined as total plasma cholesterol >200 mg/dl, LDL-cholesterol >130 mg/dl, HDL-cholesterol <35 mg/dl and plasma triglyceride >200 mg/dl.[4] Diabetic dyslipidemia is characterised by low plasma high density lipoprotein (HDL), raised plasma levels of triglycerides and low density lipoprotein (LDL). This pattern is a treatable risk factor predisposing to atherosclerosis. Diabetics are more prone to develop cardiovascular diseases. The association between diabetes mellitus (DM) and atherosclerosis is yet not entirely clear.[1] Uncontrolled T1D is usually accompanied with metabolic derangements like defective production and removal of plasma lipoproteins leading to dyslipidemia and atherosclerosis but data describing the level of awareness and management of this complication is still lacking.[5]

Uncontrolled T1D often leads to a life threatening complication called diabetic ketoacidosis (DKA). This serious outcome may also be seen in type 2 diabetes (T2D). Hypoinsulinemia results in hyperglycemia induced hyperosmolarity and polyuria. Along with water elimination via kidneys, plasma electrolytes like sodium and potassium are also lost. Hence dehydration and electrolyte imbalance are also characteristic features of uncontrolled TID.[6]

Initially insulin actions were thought to be only on peripheral tissues due to the belief that it is unable to cross blood brain barrier and non insulin dependent glucose uptake by neurons. Diabetics require therapeutic doses of insulin but insulin induced hypoglycaemia indirectly promote hunger and tempt eating. However now it has been established that insulin, not only crosses blood brain barrier but also binds to specific neuronal receptors affecting hunger and body weight. Studies have also proved that body tissue insulin sensitivity reduces with increase in body weight/body fat. The more the number of adipocytes, the more is insulin required to keep the person normoglycaemic. Hence

obesity requires intensive pancreatic activity to control blood glucose. Diabetes and obesity together make a lethal combination exerting adverse effects on blood glucose metabolism, thus further complicating the condition.7

Present research was planned to assess and compare the extent of pathophysiological disturbances leading to dyslipidemia, hormonal and electrolyte imbalances, and acid-base changes in controlled and uncontrolled T1D.

## MATERIAL AND METHODS

This was a retrospective, analytical case control study. Non-probability convenient sampling technique was used. The patients of either sex aged 18–40 years were selected from those admitted in the hospital or attending the hospital as outdoor patients at Military Hospital Rawalpindi, and Diabetic Clinics. Subjects were grouped as: Group A (control) with 20 healthy non-diabetic individuals with fasting blood glucose level <6 mmol/L and HbA1c <6% (normoglycaemic); Group B included 20 monitored diagnosed cases of T1D whose fasting blood glucose level was <6 mmol/L and HbA1c was <6% due to effective control with diet and insulin therapy; and Group C having 20 diagnosed cases of T1D whose fasting blood glucose level was >6 mmol/L and HbA1c was >6% due to poor diabetic control. Diagnosis of T1D was established according to WHO diagnostic criteria.[8]

For arterial blood gases (ABGs) measurement, whole blood (2 cc) was taken from radial artery in Heparinized syringes. Precaution was taken to avoid mixing of air bubbles in the blood sample. Samples were properly preserved in crushed ice immediately after being drawn and rapidly (<15 minutes) transported to the laboratory for analysis. Venous blood, after refrigerated centrifugation at -4 °C, was stored at -80 °C till analysed for estimation of plasma insulin and glucagon. Venous blood was analysed for plasma glucose by glucose oxidase enzymatic colorimetric method and glycosylated haemoglobin ($HbA_1c$) by micro-column method (ion exchange chromatography).[9] Plasma glucagon level was estimated by Radioimmunoassay (RIA) technique and plasma insulin level by enzyme linked immunosorbent assay (ELISA) technique.[10] Plasma sodium and potassium levels were estimated by ion selective electrode method. Arterial blood *p*H, $Pco_2$ and $Po_2$ was determined by ion selective electrode method. Bicarbonate ion concentration was calculated by using the measured parameters *p*H and $Pco_2$ in the Henderson Hasselbalch equation. Oxygen saturation was determined by use of the measured parameters of *p*H and $Po_2$ and the equation for a normal oxygen association curve.[11]

Statistical calculations were done using SPSS-15. Data were subsequently examined by independent student *t*-test. Results were expressed as Mean±SEM and $p<0.05$ was considered statistically significant.

## RESULTS

Total 60 subjects were investigated. Diagnosis of T1D was established by clinical history, WHO diagnostic criteria and laboratory investigations. There was significantlu high levels of mean plasma glucose ($p<0.001$) and glycosylated haemoglobin ($p<0.01$) in patients with uncontrolled T1D. Mean plasma insulin level was significantly reduced in both controlled ($p<0.05$) and uncontrolled T1D ($p<0.001$). Mean plasma glucagon level was significantly raised ($p<0.01$) in uncontrolled T1D. Significantly raised values of mean BMI ($p<0.05$), low plasma sodium ($p<0.01$) and raised potassium levels ($p<0.01$) were seen in uncontrolled T1D. Mean arterial blood *p*H was significantly reduced ($p<0.05$), mean arterial $Pco_2$ was significantly raised ($p<0.05$) and mean plasma $HCO_3^-$ was significantly reduced ($p<0.05$) in uncontrolled T1D. In uncontrolled T1D, mean plasma triglyceride, LDL cholesterol and total cholesterol levels were significantly raised ($p<0.01$) whereas HDL cholesterol was significantly reduced ($p<0.05$).

**Table-1: Age, plasma glucose, HbA1c, plasma insulin, plasma glucagon, BMI, serum sodium and serum potassium in groups (Mean±SEM) (*p* in parenthesis)**

| | Control | Controlled T1D | Uncontrolled T1D |
|---|---|---|---|
| Age (years) | 33.15±2.7 (0.221) | 32.4±2.7 (1.010) | 33.2±0.26 (0.990) |
| Plasma glucose (mmol/L) | 5.17±0.06 (0.191) | 5.06±0.09 (0.211) | 9.67±0.06 (0.000) |
| Glycosylated haemoglobin (%) | 5.33±0.16 (0.135) | 5.1±0.08 (0.124) | 8.63±0.3 (0.003) |
| Plasma insulin (ng/100 ml) | 37±5.4 (0.199) | 34.33±2.3 (0.04) | 29.27±2.09 (0.000) |
| Plasma Glucagon (pg/100 ml) | 55.93±4.7 (0.174) | 63.53±1.9 (0.229) | 91.53±2.19 (.007) |
| BMI ($Kg/m^2$) | 24.93±0.75 (0.303) | 23.8±0.65 (0.312) | 29.47±0.71 (0.03) |
| Serum sodium (mmol/L) | 138.4± 0.29 (0.188) | 137.07±0.67 (0.291) | 133.27±0.53 (0.009) |
| Serum potassium (mmol/L) | 3.9±0.02 (0.619) | 3.9±0.07 (0.619) | 4.44±0.11 (0.005) |

**Table-2: Acid-base status and lipid profile of subjects (Mean±SEM) (*p* in parenthesis)**

| | GROUP A | GROUP B | GROUP C |
|---|---|---|---|
| Arterial blood *p*H | 7.43±0.15 (0.107) | 7.42±0.04 (0.112) | 7.37±1.3 (0.043) |
| $Pco_2$ (mm Hg) | 38.18±0.48 (0.065) | 38.83±0.46 (0.098) | 41.63±0.35 (0.020) |
| $Po_2$ (mm Hg) | 80.87±2.3 (0.400) | 78.8±1.8 (0.433) | 78.6±1.7 (0.386) |
| Plasma $HCO_3^-$ (mmo1/L) | 26.74±0.23 (0.143) | 24.34±0.32 (0.140) | 23.5±0.31 (0.045) |
| Triglyceride (mmol/L) | 1.14±0.48 (0.231) | 0.95±0.9 (0.212) | 1.57±2.4 (0.003) |
| HDL-C (mmol/L) | 1.39±0.89 (0.094) | 1.37.1±0.58 (0.233) | 1.31±0.72 (0.006) |
| LDL-C (mmol/L) | 3.05±1.3 (0.156) | 3.03±0.2 (0.301) | 3.56±1.3 (0.005) |
| Total Cholesterol (mmol/L) | 5.1±2.1 (0.113) | 4.93±1.8 (0.889) | 5.81±0.96 (0.003) |

## DISCUSSION

Uncontrolled T1D is the condition which is not being effectively treated, causing marked persistent hyperglycemia leading to severe and even fatal diabetic complications like cardiovascular accidents or stroke. In present study marked hyperglycaemia in group C patients confirmed poor diabetic control as compared to other two groups. Hence this group would be at a higher risk to develop diabetic complication like cataract, atherosclerosis, retinopathies, renal dysfunctions, neuropathies, coma and even death.[12]

Hypoinsulinemia and relative hyperglucagonemia in uncontrolled T1D lead to unopposed biochemical actions of glucagon. Therefore significant uncontrolled hyperglycaemia persists resulting in exacerbations of diabetic complications. Unfortunately no therapeutic way to regulate plasma glucagon level exists. Hence the only way to avoid hyperglucagonemia induced complications is good diabetic control with diet and therapeutic doses of insulin or oral hypoglycaemic drugs.[13] Lee *et al* also proved that glucagon induced metabolic disturbances could be prevented by blocking glucagon actions with the help of streptozotocin in type 1 diabetic mice.[14] Wahid *et al* showed similar result by proving that as insulin to glucagon ratio decreases, diabetes worsens leading to development of diabetic ketoacidosis (DKA).[15] Hormonal imbalance especially in uncontrolled diabetes requires immediate attention and intensive management to avoid worse consequences.

BMI gives an idea of body fat depots. Uncontrolled diabetics were found to be overweight. This alarming situation needs to be addressed as more BMI worsens the diabetes. A research study has shown that risk of diabetic dyslipidemia is directly proportional to BMI. Moreover if BMI is more than 30, fatality risk also rises.[16] Onset of diabetic complications is adversely associated with high BMI. Hence appropriate attention should be given to this aspect. Awareness campaigns can help to educate diabetics about association of diabetic control and weight reduction.

In present study significant hyponatremia seen in patients with uncontrolled T1D confirmed the findings of previous studies that uncontrolled hyperglycaemia and hyperosmolarity leads to urinary loss of sodium. Significant hyperkalemia seen in uncontrolled T1D is due to the hyperglycaemia induced susceptibility to hyperkalemia. Increase urinary potassium loss leads to seeping of potassium from cells into plasma resulting in apparent hyperkalemia.[17] Due to diabetic nephropathies and compromised renal functions surplus potassium stays in blood as hyperkalemic state. However, no such potassium imbalance was observed in diabetics with controlled blood glucose level. Hypoinsulinemia, either due to inadequate insulin production or insulin resistance, enhances lipolysis. Free fatty acids are used as body fuel instead of glucose. Preference of fatty acids as energy source leads to over production of ketone bodies. Accumulation of keto-acids lowers *p*H of body fluids leading to acidemia. This is another contributing factor in hyperkalemic state seen in uncontrolled T1D.[18] Moreover, there is evidence that in uncontrolled T1D, hypoinsulinemia reduces utilisation of ketone bodies (acetoacetate and β-hydroxybutyrate) by muscles and at the same time hyperglucagonemia enhances production of keto-acids due to its ketogenic effect. Excessive accumulation of keto-acids lowers arterial blood *p*H and diabetic is more prone to develop metabolic acidosis leading to DKA. Raised $Pco_2$ was also a contributing factor in acidemia found in uncontrolled T1D. Combined effect of all these factors leads to the development of life threatening condition called diabetic keto-acidosis (DKA). DKA may also be seen in T2DM when exposed to stress or physical illness. Serum $HCO_3^-$ level was significantly decreased in patients with uncontrolled T1D.[19]

Diabetic dyslipidemia was a characteristic finding in patients with uncontrolled T1D. Defective insulin production and hyperglycaemia alters plasma lipid profile in T1D. If diabetes is not properly managed and patients have persistent hyperglycaemia, several complications worsen the life of diabetics like cardiac diseases and atherosclerosis. Death rate is significantly higher in diabetics with persistent hyperglycaemia than non diabetics. Data proves that approximately 68% diabetic mortality in 2004 was due to cardiac disease, and in 16% cases cause of death was stroke.[20] Diabetic atherosclerosis causes decreased blood circulation resulting into peripheral artery disease and neuropathies leading to amputation. There is an established relationship between T1D, hypoinsulinemia, and dyslipidemia. Studies have also proved that in uncontrolled T1D insulin administration can rectify lipid profile. Moreover, disturbed lipid profile is also detected before onset of diabetes when insulin production is defective but plasma glucose is normal.[21] Hence conclusion can be safely drawn that hypoinsulinemia and hyperglycaemia can be the main causes of diabetic dyslipidemia observed in present study.

Type 1 diabetics are not blessed with ability to self control blood glucose level due to destruction of pancreatic beta cells. Hence the ultimate objective in treating the diabetics should be to keep them normoglycaemic to avoid the onset of life threatening complications. Otherwise if hyperglycaemia is not corrected, they will lose electrolytes, dehydrate, develop dyslipidemia and suffer from other complications.[17,21]

## CONCLUSION

In order to lead life free from diabetic complications, diabetics must be educated about significance of

treatment goals so they should go all-out to achieve excellent glycaemic control. Diabetics must get their biochemical and hormonal assessments done regularly along with regular checkups to know the response and efficacy of treatment. Special attention must be paid to diabetic dyslipidemia, as it remains undiagnosed in most of the patients with uncontrolled T1D.

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## Address for Correspondence:

**Dr. Maryam Wahid,** Prof & Head of Dept of Biochemistry, Foundation University Medical College, Islamabad.
**Tel:** +92-51-5789465, **Cell:** +92-332-5335447
**Email:** maryamwahid92@hotmail.com