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Physiological and Prophylactic Effectof C-Peptideand Insulinon Renal Functionsin Experimental Diabetic Rats

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Abstract

The present study was undertaken to explore the effects of exogenous administration of c-peptide and/or insulin on certain renal function parameters of experimentally induced diabetic rats.Intraperitonealy injected (streptozotocin60 mg/kg body weight) rats were used. Diabetic rat groups were subjected to exogenous injection of insulin either alone or in combination with c-peptide for 6 weeks. Fasting blood samples were collected from all rat groups at 15 days intervals for monitoring the blood level of glucose, urea, creatinine, uric acid and c-peptide. Also, post 24 h urine was collected by using metabolic cages and used for determination of urinary creatinine clearance, micro-albumin, nitric oxide, sodium and potassium. Results obtained revealed that treatment of diabetic rats with c-peptide combined with insulin was associated with a noticeable improvement in kidney function parameters of diabetic rats as compared with their injection alone. The administration of a combination of c-peptide and insulin could be considered as aprophylactic tool to prevent or relieve the incidence of renal dysfunction usually associated with complicated diabetic patients, as c-peptide positively affects physiological renal functions,additional studies at cellular and molecular levels are also needed.
Keywords: C-peptide, Diabetes, Insulin, Kidney function, Urine.

Introduction

Diabetes mellitus is a disease with increasing global public health significance, prevailing in two general types; Type-I and type- II (WHO, 2006). Onset of most diabetic complications such as nephropathy, neuropathy, retinopathy and hepatopathy are attributed to hyperglycaemia-induced oxidative stress, due to buildup of reactive oxygen species (ROS) occurring either from excessive production of ROS or low antioxidant defense or both (Aly *et al.*, 2010 and Mirza *et al.*, 2013).

About 30 – 40 % cases of type 1 or type 2 diabetes exhibit on-set nephropathy, and within 10 years, end-stage renal disease (ESRD) progresses in 50% of type-1 diabetic patients with overt nephropathy (American Diabetes Association, 2004 and Lee , 2005). Type-1 diabetes is frequently associated with development of glomerular hyperfiltration early in the course of disorder (Palatini *et al*., 2012). In contrast, type-2 diabetics, in which

insulin/C-peptide levels are either normal or higher, does not develop glomerular hyperfiltration (Wahren *et al.*, 2012).

Even after rigorous insulin treatment to maintain normal blood glucose levels, a substantial majority of patients still develop complications, as indicated by diabetes control and complications trial, indicating that not hyperglycemia alone contribute to the development of diabetic nephropathy (David *et al.*, 2011 and Mirza *et al.*, 2013).

It is well known that connecting (C) peptide is important in insulin synthesis. C-peptide is a 31 amino acid peptide bridging the insulin A and B chains of proinsulin. It is released with insulin into the portal circulation following cleavage of proinsulin. C-peptide is considered to possibly exert physiological effects for the therapy of diabetic neuropatghy and nephropathy, as suggested by many studies on C-peptide deficient patients. Researches have revealed that C-peptide, following binding to the cell membranes of a variety of tissues, initiates a cascade of specific intracellular signals (Yosten *et al.*, 2014).

C-Peptide is rather a more reliable measure of endogenous insulin secretion than insulin and since the mid-1970s, use of C-peptide as a stand-in marker for evaluation of type 1 and type 2 diabetes progress, as well as the effects of modules designed to preserve and improve residual β-cell function(Wahren *et al.*, 2012 and Shaw *et al.*, 2014).

This research was intended to explain the physiological effects of exogenous administration of C-peptide and/or insulin by measure of certain renal endpoints in experimentally induced diabetic male rats.

Materials and Methods

Animals:

Fifty Sprague-Dawley male rats of average weight 200 g were used. Diabetes was induced by intraperitoneal injection (IP) of 60 mg/kg body weight of streptozotocin and was verified by testing blood samples for hyperglycemia (> 300 mg/dl), 48 h post induction. Forty rats with blood glucose level exceeding 300 mg/dl were categorized as diabetic rats. The institutional ethical committee approved the research procedures used in this study. Experimental rats were further categorized into the following groups:

Group I /Control group / Non-Diabetic rats: (n=10) these were daily injected subcutaneously (SC) with 0.1 ml of isotonic saline and twice weekly with IP injection of 1 ml isotonic saline for 6 weeks.
Group II / Non–treated diabetic rats: (n=10) these were daily injected (SC) with 0.1 ml of isotonic saline and twice weekly with IP injection of 1 ml of isotonic saline for 6 weeks.
Group III / Insulin-treated diabetic rats: (n=10) these were daily injected SC with 2U insulin (Mixtard, Novo Nordisk) for 6 weeks.
Group IV / C-peptide-treated diabetic rats: (n=10) They were injected IP twice weekly with 20 ng/kg body weight of C-peptide (Monobind inc. Lake Forest, USA) for 6 weeks.
Group V / Insulin and C-peptide-treated diabetic rats: (n=10) they were injected with C-peptide and insulin as III and IV groups for 6 weeks.

Blood Sampling:

Individual fasting blood samples were collected at 9 am from rats of all experimental groups every 2 weeks up to six weeks by orbital sinus puncture (3 samples), under ether anaesthesia. After blood clotting, serum separation was done by centrifugation at 3000 r.p.m for 15 minutes and kept at -20°C till next biochemical assays. Serum levels of urea, uric acid and creatinine were measured colorimeterically (Rock *et al.*, 1987, Young, 1990, Al-Hamdani, 2010, and Mundim *et al.*, 2007). C-peptide level was measured by using enzyme immunoassay

technique (Shibasaki *et al*., 2010 and Abellan*et al.*, 2009). Concentrations of sodium and potassium were determined according to Varely (1976) using flame photometer-FP 20 (SEAC – Radim company, Italy, S/N: 701111). Blood samples collected for measurement of fasting plasma glucose level were assessed colorimetrically.

Collection of 24 hr. urine:

Twenty four hours urine samples were collected every 2 weeks starting from the 4th week post induction of diabetes from rats of all groups by using metabolic cages. Urine were used to determine creatinine clearance (Young, 1990), microalbumin (Cambiaso *et al.*, 1988), nitric oxide (Montgomery and Dymock, 1961), sodium and potassium levels (Varely, 1976).

Statistical analysis:

Data were analyzed using ANOVA test to analyze the differences among groups using general linear model procedure (SAS) at significant level of ($p< 0.05$).

Results

Data presented in Figure (1) showed that blood glucose concentration of diabetic non-treated rats was significantly higher than those of other experimental groups ($P<0.05$). Treatment with insulin, alone or in combination with c-peptide, significantly reduced glucose level to be comparable with that of control rats. Meanwhile, glucose level of c-peptide treated diabetic rats alone was significantly higher than its level in control and other treated groups ($P < 0.05$).

Also, tabulated data indicated that C-peptide level in non-treated diabetic rats or insulin treated diabetic rats was noticeably lower than that of control rats ($P < 0.05$). Moreover, rats treated with C-peptide exhibited a substantial higher level of C-peptide as compared with other experimental groups.

However, blood levels of renal parameters; urea, creatinine and uric acid in diabetic non-treated rats were comparatively high than rats of all experimental groups ($P < 0.05$).

In addition, urea level significantly elevated in insulin-treated and /or C-peptide-treated rats, comparable with control rats, although its level was significantly reduced in treated groups, comparable with diabetic non-treated rats ($P < 0.05$). C-peptide, alone or in combination with insulin, significantly reduced creatinine and uric acid levels to reach control one ($P < 0.05$).

Figure (2) showed that creatinine clearance of diabetic non-treated rats was significantly decreased comparable with control or treated rats ($P < 0.05$). Combination of insulin and C-peptide significantly increased creatinine clearance to reach control value ($P < 0.05$), however, Insulin or C-peptide alone also did increase creatinine clearance as compared with diabetic non-treated rats although, it did not reach to control value ($P < 0.05$).

In addition, urinary microalbumin level was significantly increased in non-treated diabetic rats in comparison with control or treated rat groups ($P < 0.05$).

Insulin or C-peptide, alone or in combination, significantly decreased creatinine clearance as compared with diabetic non-treated rats ($P<0.05$), although it does not reached to control value. However, no significant alterations were recorded in urinary nitric oxide level among all experimental groups.

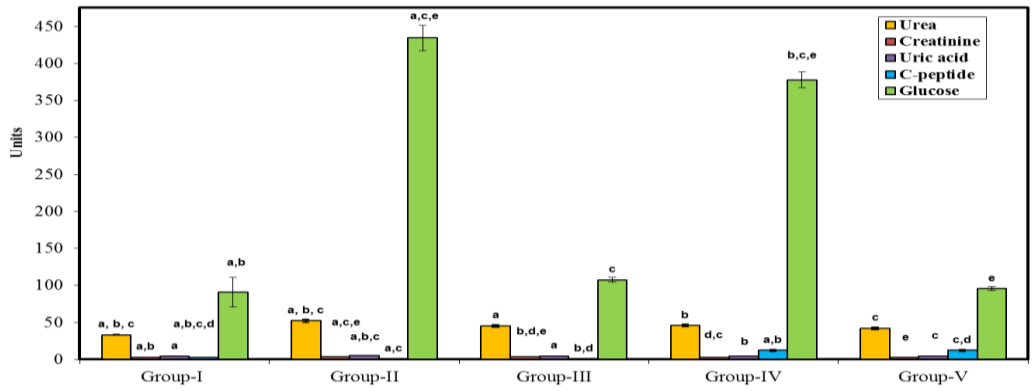

Figure 1: Certain renal blood parameters, C-peptide and glucose levels of insulin and/or C-peptide treated diabetic rats for 6 weeks.

Data represent overall means of three blood samples collections at 2nd, 4th, and 6th weeks, N=10. - Overall means within the same parameter having the same letters are significantly different at P < 0.05. NS: Non-significant. **Unit**: Urea mg%, Creatinine mg%, Uric acid mg%, C-peptide ng/ml, Glucose mg.

Insulin or C-peptide, alone or in combination, significantly decreased creatinine clearance as compared with diabetic non-treated rats (P<0.05), although it does not reached to control value. However, no significant alterations were recorded in urinary nitric oxide level among all experimental groups.

Also, data indicated that levels of urinary sodium and potassium were significantly increased in diabetic non-treated rats as compared with other experimental groups (P < 0.05). Treatment with insulin or c-peptide alone significantly decreased their levels as compared with diabetic non-treated rats (P < 0.05). Combination between insulin and C-peptide significantly decreased their levels to be similar to that of control rats.

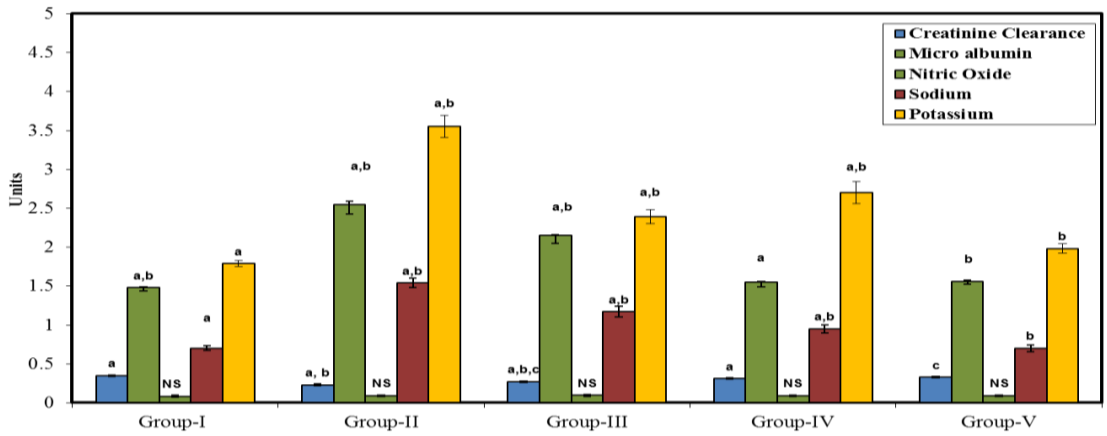

Figure 2: Certain Urine parameters of insulin and/or C-peptide treated diabetic rats for 6 weeks.

Data represent overall means of three blood samples collections at 2nd, 4th, and 6th weeks, N=10. Means within the same parameter having the same letters are significantly different at P < 0.05., NS: Non-significant**. Unit**: Creatinine Clearance ml/min, Micro albumin mg/L, Nitric Oxide µmol/L, Sodium mmol/day, Potassium mol/day.

Discussion

Quantification of C-peptide using standard conditions results in specific, accurate and clinically authenticated measurement of β-cell function and can be used in therapeutic trials designed for type 1 diabetes patients in maintaining or improving endogenous insulin release (Palmer *et al.*, 2004). Reportedly, C-peptide reverse the elevated glucose in some tissues and hence can be used a potential therapeutic tool in complication arising from diabetes (Yosten*et al.*, 2014). Signaling properties of C-peptide has also been researched (Hills and Brunskill, 2009).

Data revealed that blood glucose level was significantly decreased in all treated groups throughout the experimental periods. The elevated blood glucose level in such non-treated diabetic rats may be the effect of streptozotocin which selectively damages the pancreatic β-cells resulting in hyperglycemia (Tesch and Allen, 2007). The synergism between glucose metabolism and mineral deficiency, specifically chromium, in the body is also greatly affected by abnormality in insulin levels as it poses risk of onset insulin resistance (Carneiro *et al.*, 2013).

The obtained results indicated that C-peptide treatment, either alone or combined with insulin was associated with a reduction in blood glucose level. These may be attributed to the stimuli of C-peptide on glucose utilization through stimulation of GLUT-4 (skeletal muscle glucose transport) and not through insulin receptors, or the activation of tyrosine kinase or Phosphoinositide 3-kinases (PI3-kinase) activation in diabetes (Li *et al.*, 1999). Moreover, the capability of C-peptide on phosphorylating the insulin receptors and insulin receptor substrate 1 (IRS-1) may be also further included (Li *et al.*, 2001).
In the present study, results indicate that an improvement in kidney function parameters was associated with administration of either insulin or C-peptide alone or in combination; there were a significant decrease in the levels of blood urea, creatinine, uric acid, urinary microalbumin, sodium and potassium together with a significant increase in creatinine clearance. These patterns of results were clear in all treated diabetic rat groups.

Gayathri and Kannabiran (2009)reported significant increase in urea, uric acid and creatinine levels in diabetic rats. The present results were found to be coincided with such finding. Kaleem *et al.*, (2008) attributed the elevation of urea, uric acid and serum creatinine levels in streptozotocin diabetic rats to renal damage that resulted from irregular glucose regulation with enhanced glucose and glycosylated protein tissue levels, haemodynamic variations within the kidney tissue and enhanced oxidative stress. Diabetic nephropathy being a progressive complication leads to severe renal malfunction marked by microalbuminuria advancing into macroalbuminuria (Cade, 2008). Glomerular hyperfiltration induced stress on kidneys often results in ESRD which may lead to dialysis or kidney transplant. Similarly, Gayathri and Kannabiran (2009) reported that elevation of urea, uric acid and serum creatinine levels may have been due to streptozotocin induced metabolic abnormalities, as well as, renal malfunction. Also Saeed *et al.*, (2008) added that elevation of these parameters was due to renal dysfunction as urea and serum creatinine are reliable markers of renal dysfunction. While, Anwar and Meki, (2003) attributed increase of uric acid in diabetic rats to; metabolic disorder reflected in increased actions of xanthine oxidase, a metabolic enzyme associated with pathogenesis of hyperglycemia, involved in production of ROS, may be more so in insulin-sensitive tissues (Bravard *et al.*, 2011); or in some cases, to protein glycation, which results in muscle atrophy and increased release of

purine, and ultimately increased activity xanthine oxidase and uric acid levels.

Creatinine clearance was significantly low in streptozotocin diabetic rats (De Cavanagh*et al.*, 2001). These findings agree with the obtained results. Murali *et al.* (2003) attributed the decrease in creatinine clearance to hyperglycemia that causes osmotic diuresis and depletion of extracellular fluid volume.
The present study revealed that urinary sodium and potassium levels were found to be significantly increased in streptozotocin diabetic rats. The same findings were obtained by Rebsomen *et al.*, (2006), who reported that the increased urinary sodium levels were explained due to osmotic effect of glucosuria while urinary potassium levels were attributed to the increase in tissue breakdown, osmotic diuresis and increased distal delivery of sodium that could further augment urinary excretion of potassium.

Melin *et al.*, (2002) reported that insulin treatment reduces renal alterations such as tubular vacualization, glomerular basement membrane thickening and disturbed renal function that was recorded in kidneys of streptozotocin diabetic rats. These finding might confirm and support the obtained results. C-peptide administration has been reported to have hypoglycemic action (Nordquist *et al.*, 2007). Consequently, administration of C-peptide combined with insulin means a synergistic hypoglycemic mechanism that was cooperated in glycemic control, such suggestion might be agree with the hypothesis of Wang *et al.* (2008) who reported that tight glycaemic control reduces the onset and progression of diabetic nephropathy and also could support the present results.

Moreover,Nordquist and Wahren (2009*)*demonstrated that C-peptide treatment in diabetic patients decreased glomerular filtration rate. Furthermore, microalbuminuria, a specific indicator of diabetic nephropathy, decreased in patients receiving insulin and C-peptide up to 4 weeks *vs* patients receiving insulin alone (Johansson *et al.*, 2000). Similar results were obtained in the present investigation and agree well with the above mentioned record.

Tsimaratos *et al.*, (2003)have reported that C-peptide may induce its action through its directly stimulating Na^+, K^+-ATPase in renal tubular segments and tubular cells, and also glomular Na^+, K^+-ATPase was suggested to be stimulated.

Hills *et al.*, (2010) have demonstrated the ability of C-peptide to reduce renal complications, such as diminished glomerular hyperfiltration, reduced microalbuminuria, and increased endothelial nitric oxide synthase (eNOS).The absence of significance concerning the urinary nitric oxide that recorded in the present study could explain that the main improvement action of C-peptide on kidney function might be exerted through stimulation of Na^+, K^+-ATPase activity, rather than through nitric oxide pathway.

Reportedly, C-peptide reverse the effects of elevated glucose in some tissues and hence can be used a potential therapeutic tool in complication arising from diabetes (Yosten*et al.*, 2014). It could be concluded that administration of C-peptide alone was associated with an improvement in kidney functions nearly be similar to that induced by insulin treatment. A combination between insulin and C-peptide could induce a more significant improvement on such physiological parameters. The action of C-peptide might be explained based on the different concepts; its hypoglycemic effect and its stimulatory role on Na^+/K^+-ATPase activity. This paper hypothesize on the clear physiologically supportive role in diabetic related complication interventions and propose further trials on clinically relevant outcomes such as glomerular filtration rate,

proteinuria, kidney histology, renal replacement therapy, and mortality.

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التأثيرات الفسيولوجية والوقائية لبادئة الانسولين والانسولين على وظائف الكلية في الفئران المصابة بالسكر تجريبيا

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المستخلص

تم إجراء الدراسة الحالية لمعرفة تأثير الإعطاء الخارجي لبادئة هرمون الأنسولين (C–peptide) مع الأنسولين على وظائف الكلية في الفئران المصابة بالسكر تجريبيًا .تم حقن الفئران بجرعة من السيتربتوزوتوسين مقدارها 60 مجم / كجم من وزن الجسم ، وقد تعرضت مجموعات الفئران المصابة إلى بادئة الانسولين وحد ه أو بالمشاركة مع الانسولين لمدة ستة أسابيع نظير مجموعتين مقارنة مصابة بالسكر وأخرى سليمة ، وقد تمَّ أخذ عينات الدم من جميع المجموعات الصائمة كل (15) يوم لمراقبة بادئة الانسولين ، سكر الدم ، اليوريا ، الكرياتين ، حمض اليوريك .

وقد أسفرت النتائج عن أن معاملة الفئران المصابة بالسكر ببادئة الأنسولين مع الانسولين عن تحسن ملحوظ في قياسات وظائف الكلية مقارنة بالمجموعة المصابة غير المعالجة .وخلصت الدراسة إلى أن الحقن المشترك لبادئة الانسولين مع الانسولين يعد آداة وقاية تمنع أو تحسن من اختلالات وظائف الكلية المرتبطة بمضاعفات الإصابة بالسكري ، ويوصى بأن يجرى دراسات سريريةوأخرى جزيئية لمعرفة الآثار والآليات الفسيولوجية لعمل بادئة الانسولين.