

Low serum creatinine levels as risk factor of diabetes mellitus: prediabetes considerations

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Summary

Objective: It has been reported that low serum creatinine level is a risk factor of diabetes. We hypothesize that should this be true, serum creatinine levels would be lower and more prevalent in prediabetes than in normal individuals.

Materials and methods: 1017 glucose tolerance tests performed at South West Pathology Service of the New South Wales Health, Australia, in 2008 were sorted into normal (control), prediabetes and diabetes based on decisive interpretation. All cases with creatinine results in the control (n=48), diabetes (n=18) and prediabetes (n=36) groups were selected.

Results: Mean levels of serum creatinine levels in the controls ($80\pm 32\mu\text{mol/L}$), diabetes ($82\pm 26\mu\text{mol/L}$) and prediabetes ($82\pm 23\mu\text{mol/L}$) were not statistically significantly different. The prevalence of low levels of serum creatinine is less in prediabetes (11%) than in the control (23%).

Conclusion: Further studies using a larger number and adjusting for confounding factors is needed to ascertain the role of low serum creatinine level as a risk factor of diabetes.

Keywords: *Prediabetes, risk factors, serum creatinine*

Résumé

Il a été reporté que le faible taux de sérum créatinine est un facteur de risqué du diabète. Nous posons l'hypothèse selon laquelle ce serait vrai, le taux de créatinine dans le sérum serait plus faible et plus prévalent dans les pré-diabètes que chez les individus normaux. En 2008, 1017 tests de tolérance en glucose ont été réalisés au service des soins pathologiques situé au sud ouest de Wales, en Australie. Les sujets étaient groupés en normale (contrôle), pré-diabète et diabète basés sur la décision de l'interprétation. Tous les cas ayant des résultats de la créatinine étaient sélectionnés chez le

groupe de contrôle (n=48), diabétiques (n=18) et pré-diabètes (n=36). Les taux moyens de créatinine dans le sérum chez les groupes étaient de ($80\pm 32\mu\text{mol/L}$) de contrôle, ($82\pm 26\mu\text{mol/L}$) chez les diabétiques et ($82\pm 23\mu\text{mol/L}$) chez les pré-diabètes n'étaient statistiquement et significativement différents. La prévalence de faibles taux de créatinine est moins chez les pré-diabètes (11%) que chez le groupe de contrôle (23%). Des études avancées en utilisant une population importante et ajustant les autres déterminants sont nécessaires pour certifier le rôle de faible de créatinine en sérum comme un facteur de risqué du diabète.

Introduction

Diabetes mellitus (DM) constitutes a major health problem worldwide and its pathogenesis follows a sequence of progression that includes prediabetes or subclinical diabetes stage preceding the diagnosis of the disease. With hyperglycaemia as a risk factor, blood glucose level is highest in DM and higher in prediabetes compared to healthy individuals. Following the report that low serum creatinine level is a risk factor of diabetes [1], we hypothesize that should this be true, serum creatinine levels would be lowest in DM and lower in prediabetes compared to normal individuals.

Research design and methods

1016 glucose tolerance tests' results, of 2008, recorded in the laboratory information system of the South West Pathology Service, Albury were sorted into four categories on the basis of decisive interpretation [1]. Five hundred and eighty-nine (589) were normal and of these 48 had serum creatinine results [2]. Two hundred and forty-six (246) were reported as consistent with impaired fasting glucose or impaired glucose tolerance and of these 36 had serum creatinine results. The N=36 were newly diagnosed prediabetics and constituted the prediabetes group in this study [3]. One hundred and sixty-nine (169) results were consistent with gestational or type 2 diabetes and of these 18 has serum creatinine result. The N=18 were newly diagnosed diabetics and constituted the diabetes group in this study [4] 12 cases

were not concluded for different reasons that made decisive interpretation impossible. The individuals with creatinine results in the three groups were selected for statistical analysis using analysis of variance (ANOVA) and student's *t*-test.

In this study, results of glucose tolerance test from our archived clinical pathology data was discretionally used as selection criteria to identify the otherwise de-identified subjects who were newly diagnosed of diabetes or prediabetes, as well as those who have laboratory evidence of normoglycaemia. Blood glucose level was part of information used in decisive interpretation of the result based on which sorting into groups has been done. Results of glomerular filtration rate estimate (GFR Est.) were determined to establish absence of laboratory evidence of renal failure, based on our laboratory's cut-off point of GFR Est. >60. However, it is assumed in the study that the confounding effect of diabetic nephropathy and/or retinopathy complications may be insignificant at this stage. As participants in this study were de-identified and the outcome of this study provides for no direct or immediate personal clinical benefit to be offered, contact with patients was not made.

Results

Comparison of creatinine levels in the controls ($80 \pm 32 \mu\text{mol/L}$), diabetes ($82 \pm 26 \mu\text{mol/L}$) and prediabetes ($82 \pm 23 \mu\text{mol/L}$) show no statistically significant difference between the groups (Table 1).

Discussion

Insulin is the principal hormone that regulates transport of glucose from blood into cells, including muscles. Deficiency of insulin or the insensitivity of the cellular receptor components play a role in the pathogenesis of all forms of diabetes mellitus. Nevertheless, diabetes is not a single disease entity. Its aetiology involves a host of factors including other genetic predisposition, obesity, other endocrine secretions beside insulin and pregnancy [2-4].

It has been reported that low serum creatinine level is a risk factor for diabetes [1]. This is a new theory that demands attention. The implication of creatinine values as a biomarker in the pathogenesis of diabetes mellitus has only been associated with renal complications, where albumin-creatinine ratio is a biomarker [5]. The new theory, which is being tested in this study by evaluation of archived clinical pathology, implies that serum creatinine levels would be lower and probably more prevalent in people with subclinical diabetes vis-à-vis prediabetes when compared to apparently normal individuals. Therefore, we sought to compare the levels of serum creatinine and prevalence of hypocreataemia in newly diagnosed diabetes, prediabetes and healthy control groups.

We report observation of serum creatinine level that is not statistically significantly different between the apparently healthy control group and clinically diagnosed prediabetes group (see Table 1). This observation is in line with the notion that diabetes

Table 1: Characteristics and central values of groups

	Control	Prediabetes	Diabetes [†]
N (f/m)	48 (27/21)	36 (20/16)	18 (8/10)
Age (years)	47±18	58±15	53±17
S. Cr. ($\mu\text{mol/L}$) Mean±SD*	80±32	82±23	82±26
S. Cr. ($\mu\text{mol/L}$) Median	74	78	79
GFR Est. Mean ± SD*	78±15	73±15	76±15
GFR Est. Median	75	82	82
Prevalence of low S. Cr. [‡]	23%	11%	28%

Key: [†]Type 2 and gestational diabetes; [‡]baseline value: <60 $\mu\text{mol/L}$; *No statistical difference between groups; GFR = glomerular filtration rate; 'S. Cr.' = serum creatinine

The observed prevalence of low levels of serum creatinine is highest in the diabetes group (28%) compared to 11% and 23% observed in prediabetes and normal groups, respectively (Table 1).

pathogenesis is unassociated with low serum creatinine levels, except in certain end-stage renal disease [6]. This report is also in agreement with a case report where elevated serum creatinine was observed in a patient who has prediabetes and kidney transplant [7].

Given diabetic nephropathy and the position of prediabetes in the pathogenesis/progression of diabetes, we could infer that our observation of higher average of serum creatinine levels plus lower prevalence of hypocreataemia in the prediabetes group does not support the report that low level of serum creatinine is associated with diabetes. Our small sample size may be a limitation and this is duly acknowledged. Furthermore, we also report a prevalence of low levels of serum creatinine that is lower in the diabetes group than in the healthy control group. Therefore, it would be necessary to rigorously and scientifically debate this theory before making a decisive position statement.

Ordinarily, a low creatinine level in the absence of abnormal albumin level could impact on the albumin-creatinine ratio, glomerular filtration rate (GFR) and the clinical usefulness of the laboratory result. It is known that homocysteine level is correlated to creatinine level and the former is not lower in prediabetes than in the controls group [8]. What this report demonstrates is that serum creatinine levels is not lower in prediabetes compared to normoglycaemia. Therefore, this study is unable to provide support of a possibility of low serum creatinine level as a risk factor in diabetes. We surmise that further research is required to substantiate the speculation.

A few cautions need to be brought to fore in any further research. This includes but not limited to the following:

- Although, serum creatinine levels are correlated with creatinine generation rate and correlates with muscle volume, study has shown that serum creatinine below a cut-off point was associated with gastrointestinal symptoms, pulmonary edema and uraemic encephalopathy [6].
- While serum creatinine is a cause of limitations in the clinical usefulness of GFR as a renal function test [9], albumin creatinine ratio has been reported to show a gradual increase with diabetes progression [5]. GFR did not show any statistical significant difference between groups in this pilot study (Table 1).
- There is inverse relationship between serum creatinine and mean kidney length, which means that serum creatinine levels will depend in part on the length of the person's kidney [10];

Prediabetes has been termed America's largest healthcare epidemic [11]. It is estimated to affect 16% adult Australians [12]. Serum creatinine is a very common laboratory test, but not currently a

consideration in the diagnosis or screening of diabetes or prediabetes. The diagnosis and management of prediabetes and type 2 diabetes continues to require reassessment to ensure that goals are attained [13]. Affirmation of the speculation that this laboratory index may be useful – or otherwise – in diabetes prediction is imperative.

We have tried to search for reports on studies that followed up on the speculation of Harita *et al.*; to no avail, which implies that this report is the first to investigate the new theory. If the publication is meant to be acted upon by the readers, or translated for clinical practice, it is thinkable that follow-up research reports vis-a-vis scholarly debates will be imperative. Thus, the contribution of this article is not speculation of any new theory, but to stimulate debate on one that is speculated. It is recommendable to do further study using larger sample size as well as adjusting for kidney size and muscle volume to ascertain low serum creatinine level as a risk factor of diabetes.

Conclusion

Our report did not affirm that low serum creatinine level is a risk factor of diabetes. To our knowledge, there has been no study that followed up on the report, which means that our report is the first to investigate the new theory. In order not to appear skeptical, we indicate a direction or implication (prediabetes) that would benefit from the theory, subject to further debate or studies to affirm the speculation.

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