# The potential therapeutic benefit of paracetamol in treatment of patients with type-2 diabetes mellitus

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## ABSTRACT

**Background: Oxidative stress may contribute to the pathogenesis of diabetes mellitus, and hyperglycemia and oxidative stress can reinforce each other. The use of antioxidant drugs, therefore, may be beneficial in treatment of diabetes mellitus and paracetamol had been shown to have antioxidant activity.**

**Objectives: To evaluate the potential role of paracetamol in type-2 diabetic patients not achieving target glycated hemoglobin (HbA1c).**

**Patients and Methods: Twenty four type-2 diabetic patients consulting the Center for Diabetes and Endocrinology in Maysan were included in this study after meeting a set of inclusion criteria. Their HbA1c was more than 7% despite the continuous use of oral antihyperglycemic drugs. Patients were treated with paracetamol 1000mg tablet once daily for one month. Blood samples were taken before, one month and three months after the start of treatments for measurement of HbA1c, C-reactive protein, C-peptide level, total antioxidant capacity and more frequently plasma glucose level (fasting/random). Another sixty patients of similar inclusion criteria were also followed for three months but without treatment with paracetamol and served as a control group.**

**Results: One month treatment with paracetamol (n=24) resulted in a beneficial effect particularly when measured two months after cessation of paracetamol treatment. Paracetamol significantly reduced HbA1c by 7.32% and random plasma glucose (RBG) by 22%, and greatly increased C-peptide by 443%. Total antioxidant capacity measured once after one month of paracetamol treatment increased by 20.2%. Unexpectedly, CRP was reduced significantly by 63.9%. The control, non- intervention group did not show significant changes in the levels of HbA1c over the three month period. Measurement of HOMA- ß C-peptide in a limited number of patients indicate that paracetamol significantly improve ß-cell function.**

**Conclusion: Paracetamol 1000mg tablet, when administered once daily for one month seem to be effective in achieving a good glycemic control in patients not achieving target HbA1c.**

## الفائدة العلاجية المحتملة للباراسيتامول في معالجة مرضى السكري من النوع الثاني

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*خلفية الدراسة:* قد يسهم إجهاد الأكسدة في مراضة داء السكري وان ارتفاع السكر في الدم وجهد الأكسدة يعزز أحدهما الأخر. لذا فان استعمال الأدوية المضادة للأكسدة قد تكون مفيدة في معالجة داء السكري وظهر ان للباراسيتامول فعالية مضادة للأكسدة.

*الهدف من الدراسة:* لتقييم الدور المحتمل للباراسيتامول في مرضى داء السكري من النوع الثاني الذين لم يبلغوا مستوى الهيموغلوبين التراكمي المستهدف

*المرضى وطرائق العمل:* شملت الدراسة ٢٤ مريضا" بالسكري من النوع الثاني والذين راجعوا المركز التخصصي للسكري والغدد الصماء في محافظة ميسان بعد استيفائهم لمجموعة من معايير ألاشتمال وكان الهيموغلوبين التراكمي لديهم أكثر من ٧% على الرغم من الاستعمال المستمر للأدوية المنقصة للسكر العالي التي تؤخذ عن طريق الفم فكانوا هم مجموعة الدراسة وتم إعطاؤهم أقراص الباراسيتامول ١٠٠٠ ملغم مرة واحدة يوميا" لمدة شهر واحد، وأخذت عينات من الدم لإجراء فحوصات الهيموغلوبين التراكمي و البروتين التفاعلي نوع سي و سي بيتايد ومستوى السكر في الدم أما عند الصوم أو بشكل عشوائي لكل مريض قبل وبعد شهر وثلاثة أشهر من بدء العلاج، وتم أيضا قياس السعة الكلية لمضادات الأكسدة قبل البدء وبعد شهر واحد من العلاج بالباراسيتامول. كما تمت متابعة ستين مريضاً أخر تنطبق عليهم معايير الاشتمال أيضا لمدة ثلاثة أشهر ولكن بدون المعالجة بالباراسيتامول واتخذت كمجموعة ضابطة.

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*النتائج:* نتج عن شهر واحد من المعالجة بالباراسيتامول تأثيرات واضحة عندما تم قياسها بعد شهرين من إيقاف المعالجة حيث قلل الباراسيتامول الهيموغلوبين التراكمي بنسبة ٧.٣٢% و مستوى السكر العشوائي بنسبة ٢٢% و زاد مستوى البيتايد سي بدرجة كبيرة وبنسبة ٤٤٣%. وزادت السعه الكلية لمضادات الأكسدة بعد شهر واحد من المعالجة بالباراسيتامول بنسبة ٢٠,٢%. وقلل وبصورة غير متوقعة من مستوى البروتين المتفاعل نوع سي بنسبة ٦٣،٩%. أما المجموعة الضابطة التي لم تعالج بالباراسيتامول فلم يظهر فيها تغير بمستوى الهيموغلوبين التراكمي على مدى ثلاثة أشهر. واظهر قياس الهوما– بيتا للسي بيبتايد في عدد محدود من المرضى ان الباراسيتامول حسن وبشكل معتد من وظيفة خلايا بيتا.

*الاستنتاج:* يبدو ان المعالجة بأقراص الباراسيتامول ١٠٠٠ ملغم ولمدة شهر كانت فعالة في الحصول على سيطرة سكرية جيدة لدى مرضى السكري من النوع الثاني غير المسيطر عليه والذين يعالجون بالأدوية الخافضة للسكر العالي التي تؤخذ عن طريق الفم.

## INTRODUCTION

Type-2 diabetes (T2D), is becoming an important health problem worldwide. The total number of people with diabetes is estimated to rise to 526 millions in 2030.[1] The prevalence of diabetes in Basrah (Iraq) was reported to be 7.43%[2] and T2D in Iraq 9.3%.[3] Oxidative stress can play a major role in the pathogenesis of diabetes mellitus; both in its onset and complications.[4,5] One of the etiological factors of insulin resistance has been linked to oxidative damage of essential macromolecules in insulin sensitive tissues.[6] Oxidative stress is greatly increased due to prolonged exposure to hyperglycemia and impairment of oxidant / antioxidant equilibrium.[7] Oxidative stress is, therefore, one of the factors that leads to T2D through beta cell dysfunction and decreased insulin secretion. On the other hand, hyperglycemia can also lead to oxidative stress. Thus, oxidative stress and hyperglycemia reinforce each other. Several laboratory and preclinical studies have demonstrated that paracetamol may have a beneficial effect on blood glucose levels, skeletal muscle function and as cardioprotective and neuroprotective agent.[8-12] These studies have suggested that these off-label applications may be derived from the ability of paracetamol to function as antioxidant.

This study, therefore, aims to evaluate the role of paracetamol in type 2 diabetic patients not achieving target HbA1c.

## PATIENTS AND METHODS

Diabetic patients consulting the Center for Diabetes and Endocrinology in Maysan (south-east of Iraq) during the period from November 2012 to April 2013 were included after meeting a set of inclusion criteria. The study protocol was approved by the College Council and Ethical Committee at the College of Medicine, University of Basrah (south of Iraq). The study is open-label, therapeutic, outpatient-based study to investigate the effect of one-month treatment with paracetamol on the glycemic control of diabetic patients. All patients were selected during their consultation to the Center for Diabetes and Endocrinology in Maysan. T2D patients not achieving target HbA1c level and diagnosed as diabetic for more than one year were recruited for the study. Their age should be 30-60 years, body mass index is 25 or more, on oral antihyperglycemic drugs (both sulfonylureas and metformin) for not less than 6 months, FPG is 126 mg/dl or more, RPG is 200mg/dl or more and HbA1c is 7% or more. They should have no contraindication to the use of paracetamol, with no associated cardiovascular diseases, and not using paracetamol, or other drugs for at least 2 weeks before being included in the study. Paracetamol (Doliprane, Sanofi, France), 1000mg tablet was given as a single daily dose in the morning after meal. Patients were seen every 2 weeks in the first month to receive the treatments, to check for compliance and to question them about possible side effects. Plasma glucose level

(fasting or random) and other laboratory investigations were also done in the mean time. Lipid profile, liver function tests, renal function tests (kits from Abbott, USA) were performed for all patients before starting treatment. All patients were already receiving metformin (Merck, France), 850mg twice daily and glibenclamide (Sanofi-Aventis, France), 5mg daily provided to them by the Center. HOMA-ß C-peptide index was calculated according to the following formula: HOMA-ß C-peptide= 20xFPC (pmol/l)/(FPG(mmol/l)-3.5).[13] SPSS (Statistical Package of Social Sciences) version 20 was used for statistical analysis. Paired t test was used to test significance of changes at 0, 1 and 3 months after the start of treatment.

## RESULTS

### 1. Characteristics of the patients

Out of the 27 type-2 diabetic patients recruited for this study, 24 managed to complete the three month-period of the study. The remaining 3 patients were not able to complete the study and had defaulted at various times of the study. The main reasons for defaulting seem to be attributed to the requirement for frequent visits and blood sampling and the far distance of their residence. Patients in the control group were selected using the same inclusion criteria and found fairly comparable with that of the study groups in terms of age, duration of diabetes, HbA1c% and other parameters **(Table-1)**.

**Table 1. Characteristics of patients recruited for this study HbA1C**

| Groups | No. | Age (mean years± SEM) | Male: female Ratio | Bmi Kg/m$^2$ | | Duration of DM (mean years ±SEM) | Family history | | level mean±SEM |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Over-weight (25-29) | Obese >30 | | +ve | -ve | |
| **Paracetamol** | 24 | 54.6±1.1 | 0.62 (5:19) | 62.5% | 37.5% | 6.1±0.65 | 54.2% | 45.8% | 8.2±0.19 |
| **Control** | 60 | 46.5 ± 0.78 | 0.53 (21:39) | 73% | 27% | 4.1±0.28 | 56.7% | 43.3% | 8.1±0.1 |

### 2.The effects of one month-treatment with paracetamol 1000mg tablet once daily on type-2 diabetic patients not achieving target HbA1c (n=24).

The mean ± SEM of HbA1c before the start of paracetamol treatment was 8.2 ± 0.19. There was no change after one month of treatment with paracetamol. While, two months after stopping paracetamol treatment, HbA1c decreased to 7.6 (a reduction by 7.32%, P = 0.008, table-2 ).

**Table 2. HbA1c level at pre-treatment and one and three months after the start of treatment of type-2 diabetic patients given paracetamol 1000mg tablet once daily for one month**

| Time with respect to paracetamol treatment | No. of patients | Mean Hba1c(%) | SEM | % Change with respect to pre-treatment level | Statistical significance* |
|---|---|---|---|---|---|
| **Pre- treatment** | 24 | 8.2 | 0.19 | --- | |
| **One month after paracetamol treatment** | 24 | 8.2 | 0.26 | --- | P = 1.0 |
| **Two months after cessation of paracetamol** | 24 | 7.6 | 0.19 | ↓ 7.32%* | P = 0.008 |

CRP decreased by 13.98% from a value of 8.8 to 7.5 mg/L after one month treatment with paracetamol. However, two months after stopping paracetamol, CRP continued to decrease reaching a value of 3.18 ± 0.26 (a reduction by 63.9%, P = 0.047). There was a significant increase in C-peptide level after one month treatment with paracetamol (an increase by 120%, P<0.001). Two months after stopping paracetamol, C-peptide level continued to rise to reach 3.8ng/ml (an increase by 442.9% compared with pre-treatment level, P < 0.001). The total antioxidant capacity was measured before and at one month after paracetamol treatment only. There was an increase in total antioxidant capacity after one month treatment with paracetamol by 20.2% (P = 0.015). The fasting plasma glucose was reduced insignificantly after one month of paracetamol treatment by 18.8%. This reduction was not increased when measured two months after cessation of treatment. There was no change in random plasma glucose after one month treatment with paracetamol treatment. However, a significant reduction occurred two months after stopping paracetamol by 22% compared with pre-treatment level (P < 0.001).

**Table 3. Summary of the effects of paracetamol 1000 mg tablet once daily for one month on different parameters in patients with type-2 diabetic patients.**

| Parameters | After one month of paracetamol treatment | Two months after stopping paracetamol treatment |
|---|---|---|
| **HbA1c (n=24)** | No change | ↓ 7.32%* |
| **CRP (n=24)** | ↓ 13.98% | ↓ 63.9%* |
| **C-peptide (24)** | ↑ 120%* | ↑ 442.9%* |
| **TAC (n=24)** | ↑20.2%* | Not measured |
| **FPG (n=5)** | ↓ 18.8% | ↓10.8% |
| **RPG (n=19)** | No change | ↓ 22%* |

**Data are expressed as percent change with respect to pre-treatment levels**
***Statistically significant difference compared with pre-treatment levels**

### 3. The non-intervention, control group

No significant changes were found in the control group over the three months of the study period as to the level of HbA1c, FPG, and RPG when measured one and three months compared with zero time.

**Table 4. The level of HbA1c, fasting plasma glucose and random plasma glucose of the control (non-intervention) group at zero time, one month and after three months from zero time.**

| Measurements | No. | 0 time | After one month | P value | After 3 months | P value |
|---|---|---|---|---|---|---|
| **HbA1c** | 60 | 8.1±0.1 | 8.3±0.19 | 0.46 | 8.33±0.15 | 0.33 |
| **Fasting plasma glucose** | 33 | 239.9±5.9 | 235.5±7.7 | 0.58 | 253 ±7.3 | 0.11 |
| **Random plasma glucose** | 27 | 301.6±9.3 | 296.1±11.2 | 0.5 | 296.7±16.5 | 0.68 |

**4. HOMA-ß C-peptide (Homeostasis Model Assessment of pancreatic Beta-cell function) index**

HOMA-ß C-peptide index was calculated in a limited number of patients according to an equation relating FPG (mmol/l) and FPC-peptide (pmol/l). Because there is no clear cut-off point is yet agreed upon in the literature below which beta-cell dysunction is determined, the mean±SEM is used in the present study to determine if there is a change in beta-cell function after treatment. The HOMA-ß C-peptide for 5 patients from the paracetamol group (for which FPG and FPC-peptide were measured) showed an increase in HOMA-ß index by 259.1% and 630% one and three months after the start of paracetamol treatment. This change is significant only at three months after the start of treatment **(Table-5)**.

**Table 5. ß-cell function index in paracetamol three group using the formula HOMA- ß C-peptide = 20 X FPC (pmol/l)/(FPG(mmol/l) -3.5) before, one month and three months after the start of paracetamol treatment.**

| Groups | No. | MEAN HOMA- ß C-PEPTIDE ± SEM | | | | |
|---|---|---|---|---|---|---|
| | | Pre-treatment level | After one month of treatment | P value | Two months after cessation of treatment | P value |
| **Paracetamol group** | 5 | 320.3 ±97 | 1150.2 ±545.1 | 0.17 | 2338.2 ±794.7 | 0.046* |

***Significant difference with respect to pre-treatment level**

**DISCUSSION**

Oxidative stress is one of the factors that leads to T2D, where both oxidative stress and hyperglycemia reinforce each other.[14] The increase in antioxidant capacity may, therefore, help in improving glycemic control in DM.[15] Several experimental and clinical studies suggest that paracetamol (acetaminophen) can improve blood glucose level which might result from its antioxidant properties.[16,17] In the present study, 1000mg of paracetamol given daily for one month to patients with T2D resulted in a statistically significant reduction in HbA1c level by 7.32%, two months after cessation of paracetamol treatment. Similar significant reductions occurred in CRP (a reduction by 63.9%), and RPG (a reduction by 22%). The 10.8% reduction in FPG was not statistically significant. Total antioxidant capacity was measured one month after paracetamol treatment increased significantly by 20.2%. Probably a significant finding is that paracetamol treatment resulted in a large increase in C-peptide level (an increase by 120% and 443% one and three months after the start of treatment in comparison to pre-treatment level). This increase which might reflect the ability of paracetamol to increase insulin release is not matched by similar changes in plasma glucose levels which might indicate insulin resistance. However, the changes in total antioxidant capacity and C-peptide levels could contribute to the favorable effect of paracetamol on HbA1c percentage; an effect that occurred in absence of factors that might disturb HbA1c level such as blood transfusion and high red blood turnover.[18] Moreover, several studies have suggested that the off-label applications of paracetamol may be derived from its ability to function as antioxidant.[8-12] The significant reduction in the inflammatory marker (CRP) is difficult to explain since paracetamol is known to have negligible anti-inflammatory effect at therapeutic doses. However, it might be related to the increased total antioxidant capacity. In

addition, it can be speculated that an interaction may occur between paracetamol and that of the oral antihyperglycemic drugs. The latter drugs had been shown to reduce CRP levels.[19] These findings agree with what is already known about the effect of paracetamol on glycemic control. Shertzer *et al*[20] found that paracetamol can normalize the increased blood glucose induced by streptozotocin in rats. Similar findings on blood glucose were found when paracetamol and tramadol were used in patients with osteoarthritis,[17] and when OTC drugs were tested for their effects on glucose tolerance.[16] In the present study, the effect of paracetamol on most measured parameters became more evident two months after cessation of paracetamol treatment. This delayed effect of paracetamol had also been found in the study of Abdullah,[21] who investigated the effect of diclofenac sodium in patients with T2DM not achieving target HbA1c.

*In conclusion*, one month treatment with paracetamol seems to have a favorable effect on the glycemic control of diabetic patients not achieving target HbA1c level. This effect became more clear two months after cessation of paracetamol treatment.

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