Glycemic control and its impact on oxidative stress biomarkers in type 2 diabetic patients treated with metformin: a cross-sectional analysis

Controle glicêmico e seu impacto em biomarcadores de estresse oxidativo em pacientes diabéticos tipo 2 tratados com metformina: uma análise transversal

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ABSTRACT

AIMS: Evidence shows that diabetic patients may be predisposed to oxidative stress owing to increased glyco-oxidation and lipid peroxidation processes in consequence of chronic hyperglycemia. However, there is dearth of information whether glycemic control positively affects the antioxidant defense system in type 2 diabetes mellitus (T2DM). We investigated the potential association between glycemic control and oxidative stress biomarkers in controlled and uncontrolled diabetic states.

METHODS: After obtaining ethical clearance, we included patients receiving metformin with glyated hemoglobin A1c <7.0% (glycemic control); newly diagnosed T2DM patients without glycemic control with hemoglobin A1c >7.0%; and apparently healthy normoglycemic individuals. The following biomarkers were determined: fasting glycemia level, malondialdehyde, glutathione peroxidase activity, catalase activity, total antioxidant capacity and total cholesterol level. The comparisons between the groups were made by ANOVA.

RESULTS: The participants were 260 in number: 80 with controlled diabetes, 80 uncontrolled and 100 controls. All participants were between 40 and 71 years old. Fasting glycemia level and hemoglobin A1c showed significant reductions (p<0.05) in controlled T2DM against the uncontrolled T2DM group, all the same both were significantly higher (p<0.05) against the controls. Likewise, malondialdehyde levels showed significant elevations (p<0.05) correspondingly in both uncontrolled and controlled T2DM against the controls, accompanied with significant reductions (p<0.05) in the antioxidative enzyme activities (glutathione peroxidase activity and catalase activity) and total antioxidant capacity levels against the controls. In addition, total cholesterol was significantly reduced (p<0.05) in controlled T2DM against both uncontrolled T2DM and controls, respectively. There were significant correlations between hemoglobin A1c and oxidative stress biomarkers (p<0.05).

CONCLUSION: There was no remarkable difference in oxidative stress states between glycemic controlled and uncontrolled T2DM, despite differences in their fasting glycemia and glycated hemoglobin levels. Our data, therefore, suggest that chronic hyperglycemia and possibly anti-diabetic medication may both equally associate with oxidative stress.

KEYWORDS: antioxidant capacity; chronic hyperglycemia; glycated hemoglobin; glycemic control; lipid peroxidation; metformin; oxidative stress; type 2 diabetes mellitus.

RESUMO

OBJETIVOS: Evidências mostram que pacientes diabéticos podem estar predispostos ao estresse oxidativo devido ao aumento dos processos de oxidação da glicose e peroxidação lipídica em consequência da hiperglycemia crônica. No entanto, há escassez de informações se o controle glicêmico afeta positivamente o sistema de defesa antioxidante no diabetes mellitus tipo 2. Esse estudo investiga a possível associação entre controle glicêmico e biomarcadores de estresse oxidativo em estados glicêmicos controlados e não controlados.

MÉTODOS: Após a liberação da comissão de ética, o estudo incluiu pacientes em uso de medicação hipoglicemiante (metformina) com hemoglobina glicosilada A1c <7,0% (diabetes controlado), pacientes recém-diagnosticados com diabetes mellitus tipo 2 sem controle glicêmico e com hemoglobina A1c >7,0% e indivíduos normoglicêmicos aparentemente saudáveis. Foram determinados os seguintes biomarcadores: glicemia de jejum, malonaldeído, atividade da glutatonia peroxidase, atividade de catalase, capacidade antioxidante total e nível de colesterol total. A comparação entre os grupos foi feita pela ANOVA.

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RESULTADOS: Foram incluídos 260 participantes: 80 com diabetes controlada, 80 não controlada e 100 controles. Todos os participantes tinham entre 40 e 71 anos. A glicemia de jejum e a hemoglobina glicosilada foram significativamente menores (p<0,05) nos diabéticos controlados comparado aos não controlados, e todos os diabéticos apresentaram valores significativamente maiores (p<0,05) que os controles. Da mesma forma, os níveis de malonaldeido foram significativamente maiores (p<0,05) nos diabéticos (controlados e não controlados), assim como valores das atividades antioxidantes (glutatona peroxidase e catalase) e nos níveis de capacidade antioxidante foram significativamente menores (p<0,05) frente aos controles. Além disso, o glicose total foi significativamente menor (p<0,05) nos diabéticos controlados quando comparados aos não controlados e controles, respectivamente. Houve correlações significativas entre a hemoglobina glicosilada e do estresse oxidativo (p<0,05).

CONCLUSÃO: Não houve diferença significativa nos estados de estresse oxidativo entre os diabéticos controlados e não controlados, apesar das diferenças nos níveis de glicose plasmática e hemoglobina glicosilada. Nossos dados, portanto, sugerem que uma hiperiglicemia crônica e, possivelmente, a medicação antidiabética pode associar-se igualmente ao estresse oxidativo.

DESCRITORES: capacidade antioxidante; hiperglicemia crônica; hemoglobina glicada; controle glicêmico; peroxidação lipídica; metformina; estresse oxidativo; diabetes mellitus tipo 2.
the antecubital vein. The blood was allowed to stand in an upright position briefly on the bench and then centrifuged at 2500rpm for 10 minutes. Fasting plasma glucose was measured immediately while other plasma and serum were then stored at -20°C until the time of analyses. All other analyses were measured within three months of blood collection. The values of glycated hemoglobin were documented.

The glucose assay was performed based on enzyme colorimetric method. In this method, glucose was oxidized by glucose oxidase to gluconic acid and hydrogen peroxide. In the presence of peroxidase, the hydrogen peroxide reacted with 4-amino antipyrine and N-ethyl-N-sulfopropyl-m-toluidine to form violet-coloured quinoneimine precipitate and measured at 520 nm [8].

Glycated hemoglobin was estimated using immunoturbidimetric latex method with commercial kit from Randox Laboratories Ltd (Diamond Road, Crumlin, Co. Antrim, Ireland). The method utilized the interaction of antigen and antibody that directly determined A1c in whole blood based on agglutination reaction [9].

Level of lipid peroxidation was determined by measuring the formation of malondialdehyde (MDA), a product of lipid peroxidation, using the method of Varshney and Kale [10]. MDA was produced from peroxidation of membrane fatty acid reacted with 2-thiobarbituric acid chromogenic reagent under acidic conditions and yielded a pink-coloured complex measured spectrophotometrically at 532nm.

Glutathione peroxidase (GSH-Px) was determined when the oxidation of glutathione was converted to reduced form by cumene hydroperoxide reagent in the presence of glutathione reductase and NADPH, with concorimunt oxidation of NADPH to NADP [11]. Absorbance of colour changes was measured at 340nm. Glutathione peroxidase concentration was determined multiplying absorbance/min by a factor of 8412.

Catalase activity (CAT) was assayed by measuring decreasing peroxide amount/amount of product formed following Aebi method [12]. One international unit (IU) of catalase represented the enzyme which decomposed one microlitre of peroxidase per minute at 25°C. Absorbance of test at 240nm was measured by spectrophotometer.

Total antioxidant capacity (TAC) was determined using the ferric reducing/antioxidant power [13]. 1.5mL of working pre-warmed 37°C ferric reducing/antioxidant power reagent (300mM acetate buffer pH 3.6; 10Mm 2,4,6-tripyridyl-s-triazine in 40mM hydrochloric acid and 20Mm ferric chloride at ratio 10:1:1) was vortex mixed with 50μL of test sample and standards. Absorbance was read at 593nm against a reagent blank. The result was reported as μmol Trolox equiv./L.

Total cholesterol (TC) was determined after enzymatic hydrolysis and oxidation. Reaction of hydrogen peroxide and 4-aminoantipyrine in the presence of phenol and peroxidase formed an indicator coloured-complex, quinoneimine, which was measured spectrophotometrically at 546nm [14].

The sample size was determined for a desired confidence level of 0.05 and 1.96 confidence interval, considering a prevalence rate of 4.6% of the T2DM in the south-west Nigeria obtained from the recent literature [6]. The minimum sample size calculated for each group was 67. The study data were statistically analyzed using the SPSS for Windows program-version 10.0 (Chicago, IL. USA). The data were expressed as mean and standard deviation. The data followed Gaussian’s distribution; between-group comparisons were assessed for nominal variables with the χ²-square test, while analysis of variance and post hoc for multiple comparisons were used to compare the quantitative variables. Statistical significance was assessed at p<0.05. Pearson’s correlation was employed in testing associations between the variables, consecutively. All calculated P-values were two-tailed.

RESULTS

The mean fasting plasma glucose (FPG) and HbA1c values in controlled T2DM, uncontrolled T2DM, and normoglycemic control groups were presented in Table 1. There were significant differences (p<0.001) comparing mean FPG and HbA1c values in controlled T2DM group against both uncontrolled T2DM and the control groups among male, female and general populations, respectively.

In Table 2, some selected biomarkers of oxidative stress in controlled T2DM against uncontrolled T2DM and control groups were presented. There was no significant difference (p>0.05) in mean MDA values between controlled and uncontrolled T2DM groups, while both were significantly increased (p<0.001) compared to the controls, similarly among the male, female and general populations, respectively. However, a gender difference between the two groups of T2DM was noted. There was a significant reduction (p<0.001) when the male group of controlled T2DM was compared against the same sex of uncontrolled T2DM group.
In addition, the mean activity of GSH-Px in controlled T2DM subjects were significantly higher (p<0.001) compared to that of uncontrolled T2DM patients, while both were significantly lower (p<0.001) compared to the controls. In the same way, a gender difference was noted; there was a significant reduction (p<0.001) when the male group of controlled T2DM was compared against the same gender of uncontrolled T2DM group.

Furthermore, there were significant reductions (p<0.001) comparing mean CAT in all population categories (male, female and general populations) of controlled and uncontrolled T2DM groups against the controls. Conversely, this enzyme activity showed no significant difference (p>0.05) between controlled T2DM and uncontrolled T2DM groups.

In addition, there was no significant difference (p>0.05) in mean TAC values between controlled and uncontrolled T2DM groups in female and the general populations, while there was a significant reduction (p<0.001) in the male category of controlled T2DM. In addition, there were significant reductions (p<0.001) comparing TAC mean values in all populations (male, female and general populations) of both controlled and uncontrolled T2DM groups against the controls.

### Table 1. The mean fasting plasma glucose and glycated hemoglobin values for controlled and uncontrolled diabetes groups and control group*

<table>
<thead>
<tr>
<th></th>
<th>Uncontrolled T2DM (n=80)</th>
<th>Controlled T2DM (n=80)</th>
<th>Controls (n=100)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>46 (57.5)</td>
<td>50 (62.5)</td>
<td>50 (50.0)</td>
<td>0.23</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 ± 12</td>
<td>58 ± 13</td>
<td>55 ± 15</td>
<td>0.65</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population</td>
<td>9.86 ± 1.13</td>
<td>5.86 ± 1.24</td>
<td>3.72 ± 0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>9.87 ± 1.14</td>
<td>5.58 ± 1.16</td>
<td>3.92 ± 0.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>9.43 ± 1.15</td>
<td>6.14 ± 1.32</td>
<td>3.52 ± 1.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glycated haemoglobin (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population</td>
<td>8.86 ± 0.44</td>
<td>5.71 ± 0.47</td>
<td>5.01 ± 0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>8.75 ± 0.46</td>
<td>5.68 ± 0.50</td>
<td>5.05 ± 0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>9.04 ± 0.34</td>
<td>5.74 ± 0.43</td>
<td>4.97 ± 0.38</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* The data were expressed as mean ± standard deviation.

** significantly different from healthy controls (Post hoc); * significantly different from controlled T2DM (Post hoc).

T2DM: type 2 diabetes mellitus.

### Table 2. Biochemical parameters of oxidative stress in controlled and uncontrolled diabetes groups against control group*

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>MDA (μmol/L)</th>
<th>GSH-Px (U/L)</th>
<th>CAT (U/L)</th>
<th>TAC (μmol Trolox equiv./L)</th>
<th>TC (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrolled T2DM</td>
<td>80</td>
<td>6.68 ± 0.82</td>
<td>5656.55 ± 1511.31</td>
<td>166.83 ± 50.79</td>
<td>990.87 ± 93.05</td>
<td>3.45 ± 0.65</td>
</tr>
<tr>
<td>Controlled T2DM</td>
<td>80</td>
<td>6.51 ± 0.72</td>
<td>6591.05 ± 1181.02</td>
<td>176.37 ± 52.30</td>
<td>964.88 ± 86.51</td>
<td>3.13 ± 0.37</td>
</tr>
<tr>
<td>Controls</td>
<td>100</td>
<td>5.45 ± 0.96</td>
<td>8844.18 ± 1175.65</td>
<td>282.63 ± 54.74</td>
<td>1334.85 ± 104.88</td>
<td>3.31 ± 0.43</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.569</td>
</tr>
<tr>
<td>Male population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrolled T2DM</td>
<td>50</td>
<td>6.73 ± 0.07</td>
<td>5495.76 ± 1335.72</td>
<td>155.60 ± 58.80</td>
<td>993.20 ± 99.37</td>
<td>3.21 ± 0.64</td>
</tr>
<tr>
<td>Controlled T2DM</td>
<td>46</td>
<td>6.48 ± 0.07</td>
<td>6870.74 ± 1034.70</td>
<td>169.65 ± 49.21</td>
<td>932.12 ± 73.69</td>
<td>2.98 ± 0.35</td>
</tr>
<tr>
<td>Controls</td>
<td>50</td>
<td>5.20 ± 0.09</td>
<td>9214.35 ± 1246.46</td>
<td>333.25 ± 19.65</td>
<td>1272.95 ± 84.20</td>
<td>3.15 ± 0.36</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.015</td>
</tr>
<tr>
<td>Female population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrolled T2DM</td>
<td>30</td>
<td>6.60 ± 0.99</td>
<td>5924.53 ± 1783.56</td>
<td>185.53 ± 25.64</td>
<td>987.00 ± 84.66</td>
<td>3.86 ± 0.43</td>
</tr>
<tr>
<td>Controlled T2DM</td>
<td>30</td>
<td>6.54 ± 0.75</td>
<td>6212.65 ± 1289.64</td>
<td>185.47 ± 56.44</td>
<td>1009.18 ± 84.56</td>
<td>3.32 ± 0.31</td>
</tr>
<tr>
<td>Controls</td>
<td>34</td>
<td>5.69 ± 0.96</td>
<td>8474.00 ± 997.44</td>
<td>232.00 ± 19.19</td>
<td>1396.75 ± 86.16</td>
<td>3.47 ± 0.45</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.015</td>
</tr>
</tbody>
</table>

* The data were expressed as mean ± standard deviation.

** significantly different from healthy controls (Post hoc); * significantly different from controlled diabetic group (Post hoc).

CAT: catalase activity; GSH-Px: glutathione peroxidase; MDA: malondialdehyde; T2DM: type 2 diabetes mellitus; TC: total cholesterol; TAC: total antioxidant capacity.
Similarly, there were significant increases (p<0.001) comparing mean TC in all population categories (male, female and general populations) in uncontrolled T2DM group against the controlled T2DM group. Conversely, there were no significant differences (p>0.05) in TC levels between uncontrolled T2DM and the controls, except in female population category where a significant increase (p<0.05) was observed.

Table 3 shows correlations between HbA1c and FPG, biomarkers of oxidative stress, and TC levels in both controlled and uncontrolled T2DM. There were statistically significant positive correlations between HbA1c and FPG, MDA, as well as TC levels in both controlled and uncontrolled T2DM, respectively. In contrast, negative correlations were observed between HbA1c and GSH-Px, TAC and CAT levels in both controlled and uncontrolled T2DM, correspondingly. However, the correlation between HbA1c and TAC in controlled T2DM was not statistically significant, while other negative correlations were statistically significant.

**DISCUSSION**

There is a dearth of knowledge to show whether glycemic control helps ameliorating or reversing the effect of possible oxidative stress and potential diabetic complications. In this study, we investigated association between glycemic control and oxidative stress biomarkers (MDA, GSH-Px, CAT and TAC) in both controlled and uncontrolled type 2 diabetes (T2DM). The values of FPG, HbA1c and the biomarkers of oxidative stress were considerably altered.

We observed remarkable increases in FPG and HbA1c levels both in controlled and uncontrolled T2DM against the controls. Nevertheless, patients on hypoglycemic treatment (controlled T2DM) had reduced FPG and HbA1c levels against the uncontrolled counterpart (Table 1). In addition, there was a strong association between FPG and HbA1c levels, regardless of glycemic control or not (Table 3). Our findings agree with the data from earlier studies [15, 16]. Meanwhile, a detailed review of mechanistic effect of hyperglycemia implicates potential over production of NADH and mitochondrial ROS that ultimately inhibit glyceraldehyde 3-phosphate dehydrogenase activity in glycolytic pathway. Consequently, inhibition of GAPDH triggers the alternative glucose metabolic (shunt/minor) pathways whose activities are normally negligible under euglycemic glycolytic pathway, but in turn generates ROS in chronic hyperglycemia thus aggravating cellular oxidative stress [17]. Again, apart from hyperglycemia-mediated induction of alternative pathways, the process of glycation (formation of HbA1c) has been associated with significant ROS production in diabetes [18].

In addition, the present study showed increased MDA levels in both controlled and uncontrolled T2DM against the euglycemic individuals. Meanwhile, MDA is an established indicator of lipid peroxidation in the process of building up oxidative stress [1]. An increase in plasma concentration of MDA level in T2DM patients, controlled and uncontrolled as shown in this study, clearly reflects oxidative stress in consequence of lipid peroxidation. In concordance with the present study, Mishra and Mishra [19] reported a positive correlation between MDA level and indices of glycemic control. In the present study, comparison between controlled T2DM against uncontrolled T2DM showed no significant difference in mean plasma level of MDA. This may be an indication of oxidative stress in diabetic patients exposed to hypoglycemic medication akin to the resultant chronic hyperglycemic effect in diabetic patients. Our findings therefore show that glycemic control may not prevent lipid peroxidation. Again, we hypothesize that some hypoglycemic agents may not prevent oxidative changes by normalization of hyperglycemia but rather serve as a possible trigger for marked lipid peroxidation in a controlled diabetic state. Our assumptions are supported by a previous study.
where it was demonstrated that, in T2DM induction of oxidative stress is largely influenced not only by hyperglycemia but also by the various classes of anti-diabetic therapeutic agents [20].

Besides, although GSH-Px activity in uncontrolled T2DM patients was considerably lower against the controlled T2DM, nevertheless GSH-Px activities in both controlled and uncontrolled DM were appreciably low against individuals in euglycemic state. This indicated that there were reduced scavenging capacities of antioxidant defense system against increased free radicals, possibly owing to glucose autoxidation, which might lead to elevation of lipid peroxidation radicals, possibly owing to glucose autoxidation, which might lead to elevation of lipid peroxidation as earlier suggested by Aouacheri et al. [21]. Further, in tandem with the present study, report shows that while GSH level reduces, cellular antioxidant capacity becomes potentially compromised yielding elevated levels of ROS that are detrimental to physiologically active macromolecules and induce oxidative damage involving [17].

Moreover, the present study also showed considerable reductions in catalase activities correspondingly in both controlled T2DM and uncontrolled T2DM patients, as opposed to normal individuals. This observation is in conformity with the previous study where low catalase activity was associated with diabetes [22]. We suggest that catalase activity could be because of enhanced production of superoxide anion radical and hydrogen peroxide, which might be in consequence of increased glucose concentration in the plasma, as above reported. Our view is supported by the report of Phaniendra and coworkers [23], where superoxide anion radical is reported as an inhibitor of catalase activity while hydrogen peroxide suggested as an established precursor of other ROS, both associated with initiation and propagation processes involving lipid peroxidation. In addition, impact of catalase antioxidant failure has long been reported in T2DM [22]. Mechanistically, chronic hyperglycemia (a hallmark of T2DM) is an endogenous stimulus that induces ROS generation, redox imbalance and activation of stress-sensitive gene expression [24]. Unfortunately, when the supposed compensatory response (involving antioxidant enzymes such as catalase and other endogenous antioxidants including GSH, superoxide dismutase, GSH-Px) becomes inadequate to maintain redox equilibrium, oxidative stress ensues and results to cellular damage [24].

Furthermore, depletions of TAC in controlled T2DM and uncontrolled T2DM patients compared to healthy controls were equally observed in this study. This agrees with an earlier study [16]. Study shows that reduced antioxidant enzyme activities and TAC depletion may increase susceptibility of diabetics to oxidative injury [25]. Oxidative injuries have been repeatedly associated with development of complications in T2DM patients [24-27]. Abnormally high levels of free radicals, lipid peroxidation and simultaneous decline in antioxidant defense mechanisms are also deleterious to cellular organelles and enzymes. Effects of oxidative-antioxidative imbalance with potential oxidative injuries are commonly associated with diabetes, neurodegenerative disorders, cardiovascular diseases, and cancers [28].

On a separate note, although we observed strong positive associations between glycemic index and cholesterol level in both controlled and uncontrolled T2DM, there were divergent outcomes in total cholesterol levels between these two patient groups against the controls, respectively. Under controlled T2DM, TC was remarkably low against the healthy individuals while there was a high TC in uncontrolled T2DM patients. Our study partly suggests that there was a metabolic derangement in uncontrolled T2DM, which signified hypercholesterolemia. Although we did not assess proportions of lipoprotein particles, it has been suggested that hypercholesterolemia is a hallmark of metabolic derangement in T2DM, which contributes to atherosclerosis through oxidative process [29]. On the other hand, in controlled T2DM our finding partly suggests that hypoglycemic agents inhibit cholesterol biosynthetic pathways that might be the culprit behind reduced TC level. In addition, in line with our finding, previous study reported inhibition of hepatocellular glucose, lipid and cholesterol biosynthetic pathways due to biguanide metformin treatment of T2DM by transcription ally suppressing steroid receptor coactivator 2 and in part activating the AMP-activated protein kinase pathway [30-32].

CONCLUSION

In this study, it is evident that both glycemic control with metformin and chronic hyperglycemia in uncontrolled T2DM have oxidative impacts on diabetics. However, the mechanism through which the anti-diabetic agents subject patients to oxidative stress is currently unknown. However, a recent report demonstrated that induction of oxidative stress in T2DM is not influenced solitarily by hyperglycemia but also by the categories of anti-diabetic drugs [20]. Our data, therefore, suggest that hypoglycemic agent (metformin) is associated with oxidative stress in the same way with chronic hyperglycemia; hence, glycemic
control with metformin may not be considered to have meaningful effect to subdue oxidative stress but worsens it.

NOTES

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Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

REFERENCES


