The Relationship between Urinary 8-Hydroxydeoxyguanosine and Metabolic Risk Factors in Asymptomatic Subjects

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Introduction

Obesity, hypertension and dyslipidemia are regarded as metabolic risk factors for atherosclerotic diseases; therefore, understanding the pathophysiology of metabolic risk factors is a key to controlling atherosclerosis [1]. The number of individuals with such metabolic risk factors is increasing [2]. Oxidative stress is generally considered to play a crucial role in these metabolic conditions [3]. Oxidative stress is a direct and/or indirect initiator of the oxidation of molecules such as lipids, proteins and nucleic acids as well as endothelial dysfunction [3, 4]. This can be seen in arthrosclerosis-free individuals, and furthermore, subsequent atherosclerotic formation causes a vicious circle via oxidative stress induced at atherosclerotic sites [3, 4]. Therefore, it is important to evaluate oxidative stress in a primary risk assessment for the prevention of atherosclerotic diseases, and more studies using oxidative stress markers are needed in preventative settings.

There are presently several methods to measure oxidative stress. 8-hydroxydeoxyguanosine (8-OHdG) is generated from guanine in DNA bases by oxidative stress [5, 6]. The measurement of 8-OHdG excreted in urine quantitatively may reflect systemic oxidative stress [5, 6]. While the respective features of the oxidative stress markers remain incompletely established, 8-OHdG is known...
Table 1. Clinical characteristics of the subjects

| Variable                        | Values   | Range min–max |
|---------------------------------|----------|---------------|
| Age, years                      | 52 ± 7   | 40–69         |
| Females/males                   | 60/30    |               |
| BMI, kg/m²                      | 25.2 ± 2.8 | 19.8–29.9    |
| Systolic blood pressure, mm Hg  | 132 ± 16 | 106–168       |
| Diastolic blood pressure, mm Hg | 78 ± 8   | 60–96         |
| Glucose, mmol/l                 | 5.0 ± 0.7 | 3.9–6.0       |
| Total cholesterol, mmol/l       | 5.4 ± 0.7 | 3.7–7.7       |
| HDL-C, mmol/l                   | 1.5 ± 0.4 | 0.9–2.5       |
| Triglyceride, mmol/l            | 1.1 (0.9–1.8) | 0.5–3.4     |
| Urinary 8-OHdG, ng/mg creatinine| 9.3 (5.8–23.2) | 0.90–48.0   |

Data are expressed as the mean ± standard deviation, median (interquartile range) or subject number.

Table 1.

Results

The subjects’ clinical characteristics are presented in Table 1. Simple correlations demonstrated that the levels of TG (positively) and HDL-C (inversely) were significantly correlated to those of 8-OHdG, respectively, as shown in Table 2. Similar results were detected when TG and 8-OHdG were not log-transformed: there was a significant and positive correlation between TG and 8-OHdG (Spearmann rank correlation test; r = 0.245, p = 0.020) as well as a significant and inverse correlation between HDL-C and 8-OHdG (r = –0.324, p = 0.001). A multiple linear regression analysis, adjusted for age, sex and all the measured variables, revealed only TG to independently show a significant and positive correlation with 8-OHdG. No other variables showed any significant correlation.

Discussion

Among several metabolic risk factors, TG was the only metabolic risk factor which weakly but significantly and independently correlated with 8-OHdG in the asymp-
tomatic subjects. The results of the present study are consistent with previous findings that show the correlation between TG and hyperoxidative stress using different markers: plasma 8-epi-prostaglandin E2-α [17]; oxygen radical generation and superoxide scavenging activity by monocytes [18]; reactive oxygen species-release by leukocytes, lipid hydroperoxides and plasma antioxidant enzymes [19]. Our present data appear to be meaningful in reinforcing and expanding these observations by establishing the use of a recent biological marker.

The significant correlation between increased levels in TG and such oxidative stress markers is also valuable because TG has not necessarily been a representative metabolic risk factor for atherosclerosis in comparison to other atherosclerotic factors such as blood pressure and cholesterol [20, 21]. The data from these studies, including the present findings, may contribute to a better understanding of the underlying role of TG in the prevention of atherosclerosis. While the detailed molecular pathways involved are yet to be determined, TG has been suggested to trigger a hyperoxidative stress environment [17–19]. These reports imply that TG may stimulate the production of reactive oxygen species and impair the antioxidant defense system [18, 19]. Moreover, some reports describe an influence of TG even greater than that of glucose [18] and cholesterol [19]. An additional mechanistic view of the relationship between TG and oxidative stress suggests that the effects of obesity on TG for oxidative stress may occur because an excessive accumulation of TG in adipocytes accompanying hypertriglyceridemia is found in obesity [22]. However, BMI was not significantly correlated with 8-OHdG in the present study. This mechanism, even though true, might be partly weakened by the fact that the Japanese (especially community-dwelling individuals such as the present study participants) have a lower BMI than Caucasian populations [23].

Although the correlations between the other oxidative stress markers and metabolic risk factors, except for TG, have previously been documented [10, 11], the present study showed weak correlations between 8-OHdG and BMI, systolic blood pressure, diastolic blood pressure, glucose, total cholesterol and HDL-C. This may be partly explained by the minor abnormality in the degree of blood pressure, plasma glucose and cholesterol in our study population in a preventative setting. Furthermore, this could affect the significant but weak correlation of TG to 8-OHdG. Although a reciprocal association between TG and HDL-C is often observed in individuals with insulin resistance and metabolic syndrome, the lack of a significant correlation of HDL-C to 8-OHdG might also be partially explained by this population. In addition, the response to the various metabolic risk factors can differ according to oxidative stress markers. Dietary habits [24] and mental states [25] may be related to the state of oxidative stress. Residual chronic diseases unidentified in the present study may also affect the measurement. These points are all considered to be limitations of this study, and therefore comparative studies using various markers, including more detailed assessments on dietary, mental and physical aspects, should be performed in future research.

**Conclusion**

TG was the metabolic risk factor found to independently have a significant and positive correlation to urinary 8-OHdG, a recently utilized biological marker of oxidative stress, in an asymptomatic population. Future studies must determine whether the management of TG can effectively prevent the production of oxidative stress.

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**Table 2. Correlations between urinary 8-OHdG and all the measured variables**

| Variable                  | r   | p      | β     | p  |
|---------------------------|-----|--------|-------|----|
| Age, years                | 0.176 | 0.097  | 0.174 | 0.096 |
| Male gender, n            | -0.032 | 0.766  | -0.018 | 0.868 |
| BMI, kg/m²                | 0.147 | 0.167  | 0.133 | 0.233 |
| Systolic blood pressure, mm Hg | 0.141 | 0.185  | -0.070 | 0.610 |
| Diastolic blood pressure, mm Hg | 0.147 | 0.166  | 0.133 | 0.292 |
| Glucose, mmol/l           | -0.107 | 0.318  | -0.123 | 0.249 |
| Total cholesterol, mmol/l | -0.155 | 0.146  | -0.136 | 0.201 |
| HDL-C, mmol/l             | -0.259 | 0.014* | -0.153 | 0.185 |
| Triglyceride, mmol/l      | 0.262 | 0.013* | 0.231 | 0.046* |

8-OHdG and triglyceride were log-transformed.

* p < 0.05. r = Pearson’s correlation coefficient; β = multiple linear regression coefficient.
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