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Negative association of obesity and its related chronic inflammation with serum glycated albumin but not glycated hemoglobin levels

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Abstract

Background: Measurements of glycated albumin (GA) as well as glycated hemoglobin (HbA1c) have been applied in order to monitor chronic glycemic control in diabetic patients. Both glycated proteins are known influenced by various factors other than glycemia. It has recently been reported that GA level is low in obese, non-diabetic children and is negatively associated with body mass index (BMI) in adult diabetic patients. However, the reasons for the connection between obesity and GA remain unknown. The aim of this study was to examine whether BMI and the obesity-related inflammatory marker plasma high-sensitivity C-reactive protein (hs-CRP) are independently associated with GA and HbA1c.
Methods: Two hundred and twelve non-diabetic subjects (158 with normal glucose tolerance and 54 with impaired glucose tolerance) were enrolled in this study. The effects of fasting plasma glucose (FPG), oral glucose tolerance test (OGTT) 2-h glucose, age, BMI and hs-CRP on HbA1c as well as those on GA were analyzed.
Results: FPG significantly correlated with HbA1c, and also significantly but weakly correlated with GA. BMI showed a significantly positive correlation with HbA1c, whereas it negatively correlated with GA. Plasma hs-CRP showed a weak positive correlation with HbA1c, whereas it was negatively associated with GA. By stepwise multivariate regression analyses, BMI and hs-CRP were negatively associated with GA but not with HbA1c.
Conclusions: These results demonstrated that BMI as well as hs-CRP were independent negative risks of GA but not of HbA1c in non-diabetic subjects. Obesity and its related chronic inflammation are involved in lower serum GA levels, but not HbA1c levels, in relation to glycemia.

Keywords: Glycation; Albumin; Hemoglobin; Inflammation; C-reactive protein

1. Introduction

All proteins in the body can be modified by non-enzymatic glycation. In diabetes mellitus the extent of the non-enzymatic glycation of proteins increases, compared with non-diabetic subjects, which may comprise at least a part of diabetic complications [1]. Among these modified proteins, measurement of HbA1c has been applied for clinical use in order to monitor chronic glycemic control in diabetic patients [2,3]. HbA1c provides an integrated measurement of blood glucose during previous 2–3 months, reflecting 120-day life span of erythrocytes [2,3]. HbA1c testing is recommended by American Diabetes Association to be performed regularly [4]. Glycated albumin (GA) measurement [5] is another method which is now widely distributed in Japan. GA reflects recent or short-term control of hyperglycemia (about 2 weeks) compared with HbA1c because of a shorter circulating half-life (17 days) of serum albumin and is not affected by erythrocyte turnover [5]. It has been shown that GA is also useful for screening for diabetes mellitus, like HbA1c [6]. In addition, GA has been shown a more sensitive index than HbA1c [7] and probably responds

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Table 1
Clinical characteristics of study subjects

	All subjects	NGT subjects	IGT subjects
N	212	158	54
Male/Female	145/67	103/55	42/12^{NS}
Age (y)	51.8±7.5	51.0±7.4	54.1±7.5**
BMI (kg/m^2)	23.6±3.1	23.3±3.0	24.4±3.5*
HbA1c (%)	5.2±0.3	5.1±0.3	5.3±0.4***
GA (%)	14.0±1.1	13.9±1.1	14.2±1.2^{NS}
Albumin (g/dl)	4.5±0.2	4.4±0.2	4.5±0.3^{NS}

Data are means±SD. NGT, normal glucose tolerance; IGT, impaired glucose tolerance; GA, glycated albumin. *P<0.05, **P<0.01, and ***P<0.001 vs. NGT subjects. NS, no significant difference.

more quickly than HbA1c to changes in glycemic control because albumin has a shorter half-life and a greater tendency to become glycated [8–10].

Measurements of HbA1c and GA are influenced by various factors other than plasma glucose. HbA1c is directly affected by erythrocyte viability: An increased erythrocyte turnover results in a lower HbA1c in relation to glycemia [11]. In addition, it is known that genetic variants and chemically modified derivatives of Hb affect HbA1c measurement by some methods [12]. GA is also influenced by half-life of serum albumin: In conditions of increased albumin turnover, GA is measured at lower level in relation to plasma glucose concentration [13]. Thus, GA measurements may be affected in patients with disorders showing abnormal albumin turnover, such as nephrotic syndrome, hypothyroidism, hyperthyroidism, and liver cirrhosis [14].

Very recently, it has been demonstrated that GA is negatively influenced by obesity in non-diabetic children [15] as well as in adult diabetic patients [16]. However, the reasons for the connection of obesity and GA level remain unknown. The aim of this study was to analyze the relation of BMI as well as obesity-related chronic inflammatory marker high-sensitivity C-reactive protein (hs-CRP) [17] with GA. In this study, we analyzed the data in non-diabetic subjects but not in diabetic patients, because in diabetic patients there were sometimes disparate results of HbA1c and GA levels due to recent fluctuations of plasma glucose and hs-CRP concentrations are prone to be affected by coexisting atherosclerotic diseases [18,19].

2. Subjects and methods

2.1. Subjects

A total of 228 Japanese subjects (158 males and 70 females) visited the Health Care Center at Kinki Central Hospital between June 16 and July 7, 2004, for health examination. All subjects had a 75-g oral glucose tolerance test (OGTT) and their glucose tolerance status was diagnosed according to the World Health Organization criteria [20]. In this study, we examined 212 subjects (145 males and 67 females) after exclusion of 12 subjects diagnosed with diabetes mellitus and 4 patients already diagnosed and treated as diabetes mellitus. Their averaged age was 51.8 y (range, 28–78 y) and averaged BMI 23.6 kg/m^2 (range, 16.2–37.5 kg/m^2) (Table 1). The institutional committee approved the protocol of this study, and all the participants gave their informed consent.

2.2. Laboratory methods

Plasma glucose and serum albumin were determined by hexokinase, glucose-6-phosphate dehydrogenase method and by bromcresol green method, respectively. HbA1c was measured with ADAMS-A1c HA-8160 (Arkray Inc., Kyoto, Japan), by HPLC [21]. Inter-assay coefficient variations were 0.85% and 0.67%, respectively, as determined in representative blood samples (5.3% and 10.4% HbA1c). Serum GA was determined by Hitachi 7600 autoanalyzer (Hitachi Instruments Service Co., Tokyo, Japan), by enzymatic method using albumin-specific proteinase, ketoamine oxidase and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) [22,23]. Inter-assay coefficient variations were 1.38% and 1.32%, respectively, as determined in representative serum samples (13.3% and 34.9% GA). hs-CRP was determined by means of latex-enhanced immunonephelometrics on a BNII Analyzer (Dade Behring, Marburg, GmbH), as described previously [24].

2.3. Statistics

All data are shown as means±SD. To correct for skewed distributions, plasma hs-CRP concentrations were logarithmically transformed. For statistical analyses, unpaired Student's *t* test or Fisher's exact test was used to compare two groups, as appropriate. To analyze the effects of explanatory variables on HbA1c, GA, and GA to HbA1c ratio (for adjustment), univariate regression analysis as well as stepwise multivariate regression analysis was performed with StatView computer program (Version 5.0 for Windows, Abacus Concepts, Berkeley, CA). In the stepwise multiple regression analysis, the F-value for the

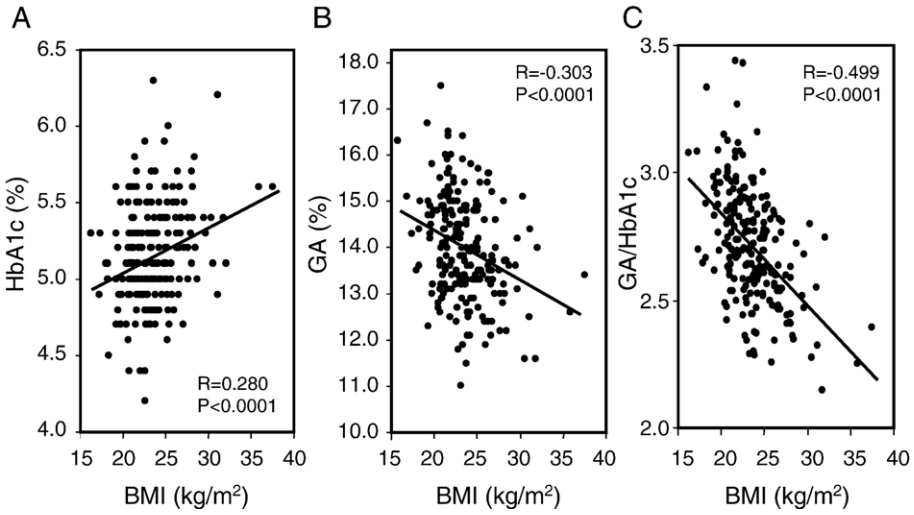

Fig. 1. Correlation of body mass index (BMI) with HbA1c (A), glycated albumin (GA) (B), and GA to HbA1c ratio (C) in 212 non-diabetic subjects.