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Association of Fructosamine to Indices of Dyslipidemia in Older Adults with Type 2 Diabetes

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Abstract

Aims—To evaluate the association of serum fructosamine values to lipid profiles and to other indices of glycemia both at baseline and over time in adults with Type 2 diabetes (T2DM).

Methods—Forty adults aged 45 or older with T2DM, not taking insulin, and an HbA1c of 6-10% were enrolled in a randomized controlled trial regarding the effects of an 8-week yoga program on glycemia and related cardiovascular disease risk indices in adults with T2DM. Fasting blood was drawn to assess glycemia (HbA1c, glucose, and fructosamine) and dyslipidemia (LDL, HDL, total cholesterol, cholesterol:HDL ratio, LDL:HDL ratio, and triglycerides) pre and post-intervention. Because the relation of fructosamine to other indices of glycemia and to lipid profiles did not differ between treatment groups either at baseline or over time, groups were pooled for analysis.

Results—Baseline fructosamine values were significantly correlated with HbA1c($r=0.77$, $P<0.0001$), glucose($r=0.72$, $P<0.0001$), LDL:HDL ratio($r=0.46$, $P=0.01$), cholesterol:HDL ratio($r=0.55$, $P=0.002$), and triglycerides($r=0.39$, $P=0.032$), but not to other lipid indices at baseline. Change in fructosamine over 8 weeks was significantly correlated with change in HbA1c($r=0.63$, $P=0.0001$), glucose ($r=0.39$, $P=0.029$), cholesterol($r=0.65$, $P<0.0001$), LDL($r=0.55$, $P=0.001$), LDL:HDL ratio($r=0.53$, $P=0.003$), and cholesterol:HDL ratio($r=0.52$, $P=0.002$), and was more strongly related to change in lipid values than were other indices of glycemia.

Conclusions—Fructosamine was significantly correlated with measures of dyslipidemia and glycemia both at baseline and over time, and may represent a relatively sensitive and low cost index of short to medium term change in both glycemia and certain lipid profiles. However, findings from this small pilot study should be interpreted with caution, and warrant replication in larger prospective studies.

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Keywords

Diabetes; dyslipidemia; fructosamine; glucose; HbA1c

Introduction

Fructosamine, a measure of glycated serum proteins, represents average glycemia over the previous 2-3 weeks, and is considered a simple, inexpensive, and reliable measure of short to medium-term change in blood glucose concentration [1-4]. In combination with fasting blood glucose, fructosamine has also been shown to be useful as an initial screen for incident diabetes [5]. Previous studies have shown fructosamine to be correlated strongly with other measures of glycemic control, including HbA1c [3], fasting glucose [6-8], and the oral glucose tolerance test [5, 9]. Elevated fructosamine levels have been associated with dementia in diabetic adults [7], with cardiovascular complications [7, 10] and oxidative stress [11] in both diabetic [7] and non-diabetic adults [7, 10-11], and with prehypertension [12] and hypertension in normoglycemic adults [11]. Increased fructosamine levels have also been prospectively associated with increased CVD morbidity and mortality in both diabetic and normoglycemic individuals [10, 13]. Although limited data from Saudi Arabian [6], Kuwaiti [14], Bosnian [8], and German [15] populations suggest that fructosamine may likewise provide a good index of lipid profiles, the relation of fructosamine to indices of dyslipidemia in diabetic populations remains unclear. Dyslipidemia is common in adults with diabetes, and is associated with significantly increased risk for CVD and other complications in diabetes [16]. Thus, a single inexpensive test that could serve as both a reliable index of glycemic control and an indirect marker for dyslipidemia could be of value in diabetes management and research, particularly in developing countries where health care resources are limited, access is poor, and the prevalence of type 2 diabetes is rapidly increasing [17]. In this brief report, we evaluate the association of serum fructosamine values to lipid profiles and to other indices of glycemia both at baseline and over time in a population of older adults with Type 2 diabetes mellitus (T2DM).

Methods

Data for this study were drawn from a randomized controlled trial regarding the effects of a yoga program vs. usual care on glycemia and related cardiovascular disease risk indices in older adults with T2DM [18]. The study population comprised 40 community-dwelling, ambulatory non-smoking adults aged 45 or older, with an established diagnosis of T2DM, not taking insulin, and an HbA1c of 6-10%. Adults with serious comorbid conditions were excluded, as were pre- or perimenopausal women. The study was approved by the university institutional review board, and all participants provided informed consent prior to study enrollment. Participants underwent a comprehensive assessment at baseline and following the 8-week intervention period; information on demographics and medical history was gathered at baseline, height, weight, and vital signs were taken, and fasting blood was drawn to assess glycemia (HbA1c, fasting blood glucose, and fructosamine) and dyslipidemia (LDL, HDL, total cholesterol, etc.). Each participant was randomly assigned to the treatment or control group based on a randomization list generated by a statistician unaffiliated with

the study; assessments and blood assays were conducted by General Clinical Research Center personnel not involved in the study and blinded to participant treatment status. Fasting blood samples were drawn by standard venipuncture technique by a trained phlebotomist using Vacutainer tubes; serum or heparinized plasma or EDTA plasma was collected as required by the procedure. Serum fructosamine was measured using a nitroblue tetrazolium (NBT) calorimetric method (Roche Diagnostics Corp., Indianapolis, IN), glucose was assessed using a Beckman glucose analyzer, and HbA1c was evaluated with a Tosoh G7 automated HPLC Glycohemoglobin Analyzer using nonporous ion-exchange high performance liquid chromatography. Lipid concentrations, including total cholesterol, HDL, LDL, cholesterol:HDL ratio, LDL:HDL ratio, and triglycerides, were measured using a Roche COBAS Mira Plus automated chemistry analyzer. Data were analyzed using PASW Statistics 18.0.0. Relationships of fructosamine to other measures of glycemia and to lipid profiles, both at baseline and over time, were assessed using Pearson's product moment correlation (or Spearman's rho for variables with skewed distribution) and stepwise regression modeling. Differences between the intervention (yoga) and control groups and between dropouts (defined as participants who did not complete the final assessment) and completers in baseline characteristics were assessed using chi square (for categorical variables), student independent samples t tests (for continuous variables with a normal distribution), or Mann-Whitney U tests (for ordinal or continuous variables with evidence of skewing).

Results

Of the 40 participants enrolled (17 men, 23 women), two participants were excluded at baseline screening due to HbA1c levels exceeding 10%. Age of the remaining 38 participants ranged from 48 to 78 years ($X = 60.6 \pm 7.8$) and included 16 men and 22 women with an average BMI (kg/m^2) of 31.8 ± 6.8 . Six participants were minority (5 African-American). Baseline serum fructosamine in this population averaged 268.8 ± 39.2 $\mu\text{mol/L}$, HbA1C averaged $6.96 \pm 1.0\%$, and fasting blood glucose averaged 139.9 ± 35.2 mg/dL . Five participants (3 women and 2 men) withdrew from the study for unknown reasons (2), or due to work (1), family (1), or health issues unrelated to yoga (1); all were non-Hispanic white. Thirty-three participants completed the final assessment (16 intervention, 17 controls). Dropouts did not differ from completers in baseline metabolic or demographic profiles. Likewise, treatment groups were similar in demographic, metabolic, and anthropometric characteristics. Because neither the relation of fructosamine to other indices of glycemia nor the correlations between indices of glycemia and lipid profiles varied by treatment group or by gender either at baseline or over time, data were pooled for analysis. Baseline and follow-up values for participants completing the study are given in Table 1.

As illustrated in Table 2, baseline fructosamine values were strongly correlated with other markers of glycemia, including HbA1c ($r = 0.77$, $P < 0.0001$) and fasting glucose ($r = 0.72$, $P < 0.0001$). Change in fructosamine from baseline to 8 weeks was likewise significantly correlated with change in HbA1c ($r = 0.63$, $P = 0.0001$) and fasting glucose ($r = 0.39$, $P < 0.03$), further supporting a close association between these glycemic indices. Fructosamine was also significantly correlated with LDL:HDL ratio ($r = 0.46$, $P = 0.01$), cholesterol:HDL ratio ($r = 0.55$, $P = 0.002$), and triglyceride ($r = 0.39$, $P = 0.03$) levels, but was not significantly related

to other lipid indices at baseline. However, participants with elevated serum triglyceride values ($>150\text{mg/dL}$) at baseline averaged significantly higher fructosamine levels vs. those with values in the normal range (310.0 ± 22.3 vs 263.7 ± 9.7 $\mu\text{mol/L}$, $P=0.04$), as did those with high total cholesterol levels (>200 mg/dL) (322.2 ± 35.4 vs 269.1 ± 8.7 $\mu\text{mol/L}$, $P=0.04$) or low HDL levels (<40 mg/dL) (317.8 ± 31.3 vs 265.3 ± 6.1 $\mu\text{mol/L}$, $P=0.02$). As illustrated in Table 2, change in fructosamine was also significantly correlated with change in several fasting serum lipid indices, including fasting cholesterol ($r=0.65$, $P<0.0001$), LDL cholesterol ($r=0.55$, $P=0.001$), LDL:HDL ratio ($r=0.53$, $P=0.003$), and cholesterol:HDL ratio ($r=0.52$, $P=0.002$); adjusting for change in BMI did not appreciably alter these relationships (Table 2), suggesting that the observed associations were not due to concurrent change in body weight (Table 2). Change in neither fructosamine nor in other glycemic indices were related to change in HDL or triglyceride levels. Notably, while fructosamine was more weakly associated with indices of dyslipidemia at baseline than was HbA1c or fasting glucose, stepwise regression analyses indicated that only change in fructosamine remained significantly related to change in the above lipid indices ($P<0.003$ for all indices), suggesting that fructosamine may represent a more sensitive index of short to medium term change in certain lipid profiles than either HbA1c or fasting glucose.

Discussion

Fructosamine is an established measure of glycemia that has been used in a number of recent studies in evaluating the effects of both short (4-12 week) and longer term (3 to 12 month) pharmaceutical [19-20], supplement [21-25], and lifestyle/educational interventions [26] on glycemia in T2DM. Previous studies have reported positive cross-sectional associations between fructosamine and other indices of glycemic control [6, 8-9], as well as between fructosamine and measures of dyslipidemia [6, 8, 14-15]. Consistent with these findings, we likewise observed strong correlations between baseline fasting fructosamine and other markers of glycemia in our pilot study in older adults with T2DM. Although to our knowledge, no previous intervention studies have specifically examined the association of change in fructosamine over time to that in lipid profiles or other indices of glycemia, several have reported improvement in fructosamine concurrent with improvement in other measures of glucose control [15, 19-24, 27] and in dyslipidemia [15, 19-22, 24, 27]. Consistent with these observations, we found change in fructosamine from 0-8 weeks to be significantly correlated with change both in other indices of glycemic control and in measures of dyslipidemia. Notably, the association of fructosamine showed a stronger association to change in certain measures of dyslipidemia over time than did other glycemic indices, suggesting fructosamine may offer a more sensitive indicator of short to medium term change in lipid profiles. Fructosamine is simpler and less costly than HbA1c [2-4, 28] and appears sensitive to change with both short and long term lifestyle, pharmaceutical, and other interventions [15, 19-24, 26-27].

Fructosamine testing may thus offer a cost-effective means to monitor both glycemic control and indirectly, specific lipid profiles, provide a reliable means of determining the effectiveness of a diabetes management plan on these indices over relatively short time periods, offer useful feedback to patients and thereby help encourage both improved patient compliance and more effective medical management. Fructosamine testing is of obvious

value in assessing the effects of short to medium term interventions on glycemia in clinical trials, and could be of potential utility as a diabetes management and research tool particularly in certain resource-poor countries where HbA1c and lipid testing may not be feasible due to logistical and economic barriers [29-30]. In light of recent studies demonstrating the benefit of tight glucose control [31], the greater sensitivity of fructosamine vs A1c to change over short to medium periods of time, and the lower cost and greater simplicity of fructosamine, reintroduction of home fructosamine monitoring might also be considered, provided concerns regarding accuracy and reliability [32] can be effectively addressed; again, this could be of particular value in countries where resources are scarce and health care access is poor.

Strengths of this pilot study include the population-based design and standardized assessment of glycemia and lipid indices at two time points. Limitations include the small sample size and restriction to adults with relatively well-controlled diabetes. Findings should thus be interpreted with caution and warrant replication in other, larger prospective studies.

Conclusion

In brief, fructosamine was strongly correlated with other measures of glycemia both at baseline and over time; change in fructosamine was also significantly related to change in lipid profiles over time and may represent a potentially useful and cost-effective measure for monitoring short to medium term change in glycemia and, indirectly, in certain indices of dyslipidemia.

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Table 1

Baseline and 8 week follow-up values: Fasting serum indices of glycemia and lipid profiles in older adults with type 2 diabetes

	Baseline (mean±SE)	Follow-up (mean±SE)
Fructosamine	269.47±7.06	264.25±7.39
HbA1c	6.90±0.18	6.86±0.18
Glucose	139.5±5.87	144.59±7.00
Total Cholesterol	171.37±6.67	163.00±6.03*
LDL Cholesterol	97.90±5.70	91.61±5.70
Triglycerides	146.56±17.45	150.28±17.92
HDL	48.91±2.15	46.10±2.15
Cholesterol:HDL ratio	3.68±0.20	3.68±0.20
LDL:HDL ratio	2.08±0.13	2.09±0.15

* Significantly different ($p<0.05$), paired t test; differences between all other values were non-significant

Table 2

Correlations of fasting serum fructosamine to glycated hemoglobin (HbA1c), fasting glucose, and fasting serum lipid values at baseline and over time in older adults with type 2 diabetes; analyses adjusted for age

		Baseline			Baseline Adjusted for BMI			Change over time			Change over time Adjusted for BMI		
		Fructosamine	HbA1c	Glucose	Fructosamine	HbA1c	Glucose	Fructosamine	HbA1c	Glucose	Fructosamine	HbA1c	Glucose
Fructosamine	Corr P	1.00	0.77 <0.0001	0.72 <0.0001	1.00	0.79 <0.0001	0.70 <0.0001	1.00	0.63 0.0001	0.39 0.029	1.00	0.62 0.0003	0.41 0.027
HbA1c	Corr P	0.77 <0.0001	1.00	0.73 <0.0001	0.79 <0.0001	1.00	0.73 <0.0001	0.63 0.0001	1.00	0.36 .043	0.62 0.0003	1.00	0.40 .032
Glucose	Corr P	0.72 <0.0001	0.73 <0.0001	1.00	0.70 <0.0001	0.73 <0.0001	1.00	0.39 0.029	0.36 0.043	1.00	0.41 0.027	0.40 0.032	1.00
Cholesterol	Corr P	0.20 .284	0.17 .370	0.00 .980	0.23 .177	0.23 .175	0.07 .678	0.65 <0.0001	0.38 .033	0.49 .004	0.65 0.0001	0.37 .049	0.53 .003
LDL	Corr P	0.15 .424	0.07 .690	-0.03 .887	0.16 .356	0.13 .455	0.01 .940	0.55 .001	0.35 .057	0.48 .006	0.63 0.0002	0.43 .019	0.57 .001
HDL	Corr P	-0.31 .087	-0.49 .005	-0.40 .027	-0.28 .098	-0.43 .010	-0.31 .067	0.13 .463	-0.15 .417	0.11 .535	0.10 .598	-0.21 .266	0.08 .678
LDL:HDL ratio	Corr P	0.46 .010	0.49 .006	0.33 .067	0.37 .028	0.42 .011	0.24 .157	0.53 .003	0.45 .012	0.40 .028	0.56 .001	0.50 .006	0.48 .008
Cholesterol:HDL ratio	Corr P	0.55 .002	0.70 <0.0001	0.43 .016	0.48 .003	0.62 .000	0.35 .038	0.52 .002	0.43 .014	0.35 .051	0.53 .002	0.45 .012	0.36 .045
Triglycerides (log)	Corr P	0.39 .032	0.57 .001	0.35 .053	0.43 .009	0.57 .000	0.37 .026	0.27 .140	0.17 .355	0.18 .330	0.22 .246	0.09 .642	0.14 .473

Note: Stratifying by obesity (BMI<30 vs BMI>=30) did not appreciably change the relation of fructosamine to other indices of glucose control; likewise, controlling for baseline BMI did not substantively change the relation between change over time in any of the analytes measured.

Corr=Correlation Coefficient