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Glucose metabolism in the idiopathic blepharoptosis: Utility of the Oral Glucose Tolerance Test (OGTT) and of the Insulin Resistance Index

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ABSTRACT

Background: Diabetes mellitus (DM), neuromuscolar, hereditary or immunological disorders are the most common identified causes of blepharoptosis. However, in about 15–25% they remained uncertain.
Objective: To determined the role of glucose metabolism abnormality in idiopathic blepharoptosis.
Methods: We identified 162 patients with unilateral idiopathic blepharoptosis and 128 control subjects. In all we evaluated a glucose and insulin levels at fasting and after 2 h-OGTT. In addition we determined insulin resistance (IR), by HOMA-index.
Results: Following a 2 h-OGTT the prevalence of undiagnosed glucose metabolism abnormality was significantly higher in blepharoptosis patients vs. control group ($P<.001$). The IR was documented in 129 patients (78%), of whom 55 (34%) had Impaired Glucose Tolerance (IGT), 36 (22%) newly diagnosed DM (NDDM) and 38 (30%) only IR. The Body Mass Index, blood pressure, serum lipids, triglycerides and smoking were not associated with an increased risk of developing ptosis. Conversely, waist circumference were significantly increased in blepharoptosis patients ($P=.003$).
Conclusions: In this study we focused on emerging evidence that prediabetic status may represent a risk factor for developing blepharoptosis. We propose that 2 h-OGTT and mainly HOMA-index should be determined as a rule in all patients with idiopathic blepharoptosis.

1. Introduction

Blepharoptosis is defined as abnormally low-lying upper eyelid margin with the eye in primary gaze, resulting is narrowing of the palpebral opening and covering part of the eye. It may be minimal (1–2 mm), moderate (3–4 mm), or severe (>4 mm), covering in the pupil entirely. Blepharoptosis can be present at birth (congenital) or develop later in life (acquired), may be due to a myogenic, neurogenic, aponeurotic, mechanical or traumatic cause [1]. Usually, blepharoptosis occurs isolated, but it may be associated with various other conditions, like immunological, degenerative, hereditary disorders, tumours, or infections. Diabetes mellitus (DM) is a common cause of ophthalmopharesis. Still, about in 15–25% it remained undetermined [2,3]. Prediabetes is defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) following a 2-h oral glucose tolerance test (2 h-OGTT) [4]. IGT is generally a manifestation of insulin resistance (IR), together with abdominal obesity, hypertension, and dyslipidemia, it is a component of the metabolic syndrome (MS) [5]. Several studies have demonstrated that IGT and other features of MS are important contributors to peripheral neuropathy [6,7]. Moreover hyperinsulinemia has been reported to cause neuropathologic changes in diabetic animals treated with an excess of exogenous insulin [8,9]. Nevertheless, the association between disorders of the glucose metabolism and neuropathy seems very likely, but the exact nature is less uncertain.

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Table 1
Features of 162 patients with "Idiopathic blepharoptosis" and 128 control subjects.

	Patients	Controls	*P* value
Number of patients	162	128	.005
Age; years	58.5 (5.2)	50.5 (6.8)	.005
Sex (m/f)	86/76	40/88	.002
Duration of symptoms; months	8.9 (0.9)	//	//
Fasting Glycaemia (mg/dl)	76 (9.2)	79 (6.8)	1.72
Fasting insulinemia (UI/ml)	18.6 (1.8)	13.4 (2.9)	.001
Waist circumference (cm)	82.3 (6.6)	79.8 (5.8)	.003
BMI	23.8 (2.3)	22 (3.4)	.26
HOMA-index	3.5 (0.6)	2.4 (0.5)	.002
Triglycerides (mg/dl)	152 (12.6)	143 (9.1)	.412
Serum lipid (mg/dl)	140 (13.6)	135 (10.1)	.79
Smokers (no.)	72	41	.25
Smoking, (cigarettes/day)	9.1 (1.8)	9.2 (2.6)	3.24
Systolic pressure; (mmHg)	117.7 (12)	119 (9.7)	.81
Diastolic pressure; (mmHg)	72.7 (6.9)	69 (9)	.79

Abbreviations: body mass index: BMI [Weight (kg)/height^2 (h^2]; HOMA index: basal glucose plasma (mg/dl) × basal insulin plasma (UI/ml)/ 405; The differences between the proportions with insulin resistance>2.7 on the HOMA formula. Values are expressed as mean (SD) unless otherwise indicated. *P-value* was evaluated after adjustment for age and sex.

This study seeks the relationship between glucose metabolism abnormality (DM, IGT, IR) in 162 patients with idiopathic blepharoptosis.

2. Methods

2.1. Patients and ethical committee approval

After a complete description of the study all patients gave their informed consent, in accordance with the official standards of the 1964 declaration of Helsinki, local laws and regulations and the study was approved by the Ethical Committee of "S. Giovanni di Dio" Hospital, Crotone, Italy. We studied prospectively 162 patients complaining of unilateral idiopathic blepharoptosis without other neurological signs and 128 control subjects, between February 2002 and May 2008. For the selection procedure we excluded patients with known causes of blepharoptosis, such as:

a. family history of neuropathy and/or miopathy;
b. miopathy and/or myasthenia;
c. distal symmetric neuropathy;
d. toxic or pharmacological exposure, alcohol overuse, coexisting medical conditions associated with miopathy, DM, disthyroidism, autoimmune conditions such as connective diseases, human immunodeficiency virus and/or other active infections;
e. abnormal results on blood tests including electrolytes, blood glucose, HgA_{1c}, renal function, liver function, complete blood count, B12 level, serum protein electrophoresis with serum immunofixation autoimmune and infective screening;
f. tumors and/or vascular disease;
g. multiple sclerosis.

We could not obtain a randomly selected control group, so we recruited normal subjects, coming from the same geographic area, ethnic background and with similar dietary habits and life style. We invited the patients to bring friends or non blood relatives with them, who did not have a known peripheric or muscular disorder, DM, family history of neuromuscular and/or endocrinologic illness.

2.2. Evaluation

A first-level check-up was carried out in patients and control subjects, by a neurologist, an ophthalmologist and an endocrinologist. Ophtalmologic evaluation confirmed blepharoptosis in all patients as "partial oculomotor palsy", while other ocular movements resulted normal. All our patients showed a unilateral ptosis of moderate–severe grade. Subsequently, patients group underwent the following tests: magnetic resonance imaging (MRI) with gadolinium of the brain, single fiber electromyography (SFEMG) and acetylcholine receptor antibody titers. Electrophysiological, neuroradiological and laboratorystic evaluations were negative in all patients. Recorded medical data for both patients and control subjects included: anamnestic data (dietary habits, life style), demographic information (age, sex), body mass index (BMI), waist circumference, glucose and insulin values at fasting and 2 h-OGTT respectively, HgA_{1c}, serum lipids, and triglyceride levels (Table 1). Procedure for the 2 h-OGTT required fasting after mid-night, obtaining a baseline fasting glucose level, and administration of the oral glucose load within a 5-min period. Blood specimens to determine plasma glucose and insulin levels were subsequently drawn at 120 min, timed from the beginning of the glucose load. IR was calculated from the homeostasis model

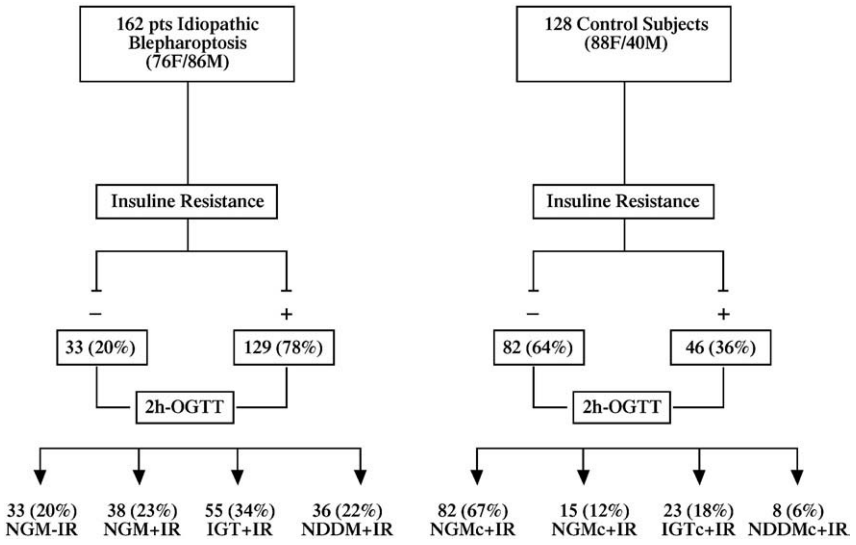

Fig. 1. Clinical features of 162 patients with "idiopathic blepharoptosis" and 128 control subjects divided in four subgroups (NGM-IR, NGM + IR, IGT + IR and NDDM + IR) according to glucose metabolism respectively by 2h-OGTT and assessment of HOMA formula. Abbreviations: *In patients*: NGM-IR, normal glucose metabolism (NGM) without insulin resistance (IR); NGM + IR, NMG with IR; NGM + IGT, NGM with impaired glucose tolerance; newly diagnosed diabetes mellitus with IR: NDDM + IR. *In controls*: NGMc-IR: NGMc + IR; NGMc + IGT; NDDMc + IR.

Table 2
Features of 162 patients with "Idiopathic blepharoptosis" and 128 control subjects divided in four subgroups (NGM-IR, NGM + IR, IGT + IR and NDDM+IR) according to glucose metabolism respectively by 2h-OGTT and assessment of HOMA formula.

	NGM-IR			NGM + IR			IGT + IR			NDDM + IR		
	Patients	Controls	*P*	Patients	Controls	*P*	Patients	Controls	*P*	Patients	Controls	*P*
No. (%)	33 (20)	82 (64)	<.001	38 (23)	15 (12)	<.001	55 (34)	23 (18)	<.001	36 (22)	8 (6)	<.001
Fasting glycaemia	63 (3.2)	70 (6.6)	.23	69.9 (6.6)	76.6 (9)	.62	82.4 (7.3)	86 (9.4)	.23	89 (11.4)	83 (9.3)	3.1
Fasting insulinemia	10 (1.1)	8.9 (1.7)	.15	19.5 (2.3)	15 (3.1)	.002	21.5 (6.2)	14.6 (2.8)	.005	23 (3.8)	15 (2)	<.001
Glycaemia 2 h-OGTT	84.6 (8)	86 (9.1)	2.3	79.4 (9.3)	74 (14.8)	.005	199 (21.4)	164 (19)	.005	262 (24.6)	221 (16)	<.001
Insulinemia 2 h-OGTT	18 (2.3)	15 (3.1)	.67	48 (5.4)	31(6.3)	<.001	46 (6.3)	32 (3.9)	<.001	49 (6.3)	35 (6.3)	<.001
HOMA Index	1.6 (0.1)	1.4 (0.2)	1.4	3.4 (0.9)	2.8 (0.4)	.005	4.4 (0.8)	3 (0.6)	.005	5.1 (2.3)	3.1 (0.3)	<.001

Abbreviations: NGM-IR, normal glucose metabolism (NGM) without insulin resistance (IR); NGM + IR, NMG with IR; NGM + IGT, NGM with impaired glucose tolerance; NDDM + IR, newly diagnosed diabetes mellitus with IR. body mass index, BMI [Weight (kg)/height^2 (h^2]; 2 h-OGTT, 2-h Oral Glucose Tolerance Test; HOMA index, basal glucose plasma (mg/dl) × basal insulin plasma (UI/ml)/405. *P-value* evaluated after adjustment for age and sex. Values are expressed as mean (SD) unless otherwise indicated.

assessment (HOMA) formula. The differences between the proportions with IR>2.77 on the HOMA formula and those without did not reach significance [10]. Patients and controls were established as having IGT if the 120-min venous plasma glucose value fell between 140 and 200 mg/dL. Criteria for new-onset DM were fasting plasma glucose level greater than 126 mg/dL or 120-min venous plasma glucose level greater than 200 mg/dL on the 2h-OGTT [4].

2.3. Data analysis

Data were expressed as mean ± SD. Patients were then compared with the controls with respect to variables representing their current status and, potentially, the aetiology of the condition. For categorical variables, this was performed by comparing distributions using χ^2 tests and for calculated variables by comparing means using *t* tests with correct test of the normal assumption required. Where these were not satisfied due to skewed data distributions, logarithmic transformations were used. Finally, to assess and allow for discrepancies among the clinical characteristics in the group comparisons and to assess the relative significance of potential aetiological variables, logistic regression was used. In all cases, a *P* value of 0.05 was considered to be statistically significant. All statistical analysis was performed with SPSS 12.0.

3. Results

3.1. Demographic features

During a period of 6 years, from 2002 to 2008, we recruited prospectively 162 patients, with isolated and idiopathic unilateral blepharoptosis. The mean age of the patients group was significantly older than the control group (58.5 ± 5.2 vs. 50.5 ± 6.8 years; *P* = .005). Eighty-six out of 162 in the patients group were men, significantly more than in the control group in which only 40 out of 128 were men (*P* = .002). Consequently, all subsequent statistical comparisons of the two groups took age and sex into account. The mean duration of symptoms was 8.9 ± 0.9 months (Table 1).

3.2. Impaired glucose tolerance and insulin resistance

The mean fasting glucose was of 76 ± 9.2 mg/dl in patients group and 79 ± 6.8 mg/dl in control group respectively (*P* = 1.72), while the mean fasting insulin was significantly higher in the patients group (18.6 ± 2.8 UI/ml 13.4 ± 2.9 UI/ml; *P*<.001). Following 2 h-OGTT, we found high prevalence of glucose metabolism abnormality in 91 (56%) patients (55 with IGT and 36 with DM) and in 31 (24%) subjects of the control group (23 with IGT and 8 with DM). After adjusting for age and sex the difference between the patients and the control was significant (*P*<.001). The IR calculated with HOMA formula, was present in 129 patients (78%), of whom 55 (34%) patients had also IGT (IGT + IR), 36 (22%) patients had also newly diagnosed DM (NDDM + IR) and 38 (23%) patients had only IR. Thirty three of the 162 (20%) patients in the blepharoptosis group had normal glucose metabolism (NGM) condition and were not IR (Fig. 1). The mean value of HOMA-index in the four subgroups was respectively: 1.6 ± 0.1 in NGM without IR patients (NGM-IR), 3.4 ± 0.9 in NGM with IR patients (NGM + IR), 4.4 ± 0.8 in IGT + IR patients and 5.1 ± 1.3 in NDDM + IR patients. In control group IR was present in 46 (36%) subjects, of whom 23 (18%) had IGT (IGTc + IR), 8 (6%) had newly diagnosed DM (NDDMc + IR) and 15 (12%) subjects had IR alone (NGMc-IR). Eighty-two of the 128 (64%) in control group were NGM without IR (NGMc-IR). After similar adjustments for sex and age, however, HOMA-index was significantly higher in patients with only IR (NGM + IR vs NGMc + IR: 3.4 ± 0.9 vs. 2.8 ± 0.4; *P* = .005) in IGT subgroups (IGT + IR vs. IGTc + IR: 4.4 ± 1.8 vs. 3 ± 0.6; *P* = .005) and mainly in DM subgroup than in the control subgroups respectively (NDDM + IR vs. NDDMc + IR: 5.1 ± 2.3 vs. 3.1 ± 0.3; *P*<.001).

Table 3
Clinical features of 162 patients with "Idiopathic blepharoptosis" and 128 control subjects divided in four subgroups (NGM-IR, NGM + IR, IGT + IR and NDDM + IR) according to glucose metabolism respectively by 2 h-OGTT and assessment of HOMA formula.

	NGM-IR			NGM + IR			IGT + IR			NDDM + IR		
	Patients	Controls	*P*	Patients	Controls	*P*	Patients	Controls	*P*	Patients	Controls	*P*
Smoking subjects no, (%)	15 (9)	16 (12.5)	.12	20 (15.6)	10 (8)	.32	22 (13)	9 (7)	.34	15 (9)	6 (5)	2.6
Smoking; (cigarettes/day)	9 (2.8)	8.4 (3.4)	.25	10.5 (3.8)	11 (1.7)	.26	8.4 (3.2)	9 (2.8)	.23	8.7 (2.2)	8.5 (3.1)	.23
BMI	23.6 (2.8)	21.6 (3.1)	2.3	24.1(3.1)	21.7 (3.4)	1.5	23.4 (4.1)	22 (2.8)	4.1	24.4 (3.2)	23.7 (4.1)	.35
Waist circumference (cm)	80.6 (5.8)	79.4 (6.5)	1.8	82.8 (4.5)	79 (5.5)	<.001	82.7 (6.6)	79.5 (4.3)	.005	82.9 (3.3)	80 (4.4)	.005
Systolic pressure (mmHg)	115 (13)	118 (7.4)	2.4	125 (9.8)	120 (6.4)	.12	117 (9.2)	114 (9.1)	.32	114 (10.2)	121 (8.3)	4.3
Diastolic pressure (mmHg)	72 (8.8)	68 (4.6)	3.3	75 (8.1)	71 (7.7)	.21	68 (7)	70 (4.3)	.54	74 (8.2)	69 (7.9)	3.3
Triglycerides (mg/dl)	144 (15)	131 (11.4)	2.6	149 (14)	152 (9.1)	.54	152 (16)	148 (13.1)	.61	165 (19)	141 (10.1)	3.7
Serum lipid (mg/dl)	134 (21)	129 (8.9)	2.2	140 (16)	134 (10.1)	2.4	132 (15)	138 (8.6)	.15	151 (15.2)	140 (13.4)	3.6

Abbreviations: NGM-IR, normal glucose metabolism (NGM) without insulin resistance (IR); NGM + IR, NMG with IR; NGM + IGT, NGM with impaired glucose tolerance; NDDM + IR, newly diagnosed diabetes mellitus with IR. body mass index, BMI [Weight (kg)/height^2 (h^2]; 2 h-OGTT, 2-h Oral Glucose Tolerance Test; HOMA index, basal glucose plasma (mg/dl) × basal insulin plasma (UI/ml)/405.
P-value evaluated after adjustment for age and sex. Values are expressed as mean (SD) unless otherwise indicated.

3.3. Clinical features

At presentation the mean BMI for all four subgroups of patients with idiopathic blepharoptosis was similar ($P=3.2$), without significantly difference vs. control ($P=.26$). The waist circumference, after the adjustment for age and sex, was significantly higher in all subgroups of patients with IR than in the controls ($P=.003$). After similar adjusting for BMI as well as age and sex, the mean values for blood pressure and serum lipid were not significantly different to the controls ($P=.79$). The smoking use defined respectively as cumulative cigarettes/day was similar for several subgroups of patients and controls. There was no statistical difference between those groups ($P=3.24$). Smokers number was greater in the patients than in the controls (72 vs. 41), but after adjusting for age and sex, this difference was not significant ($P=.25$). The mean values of triglycerides were a small and not significant increase only in the patients subgroup with DM + IR vs. control (165 ± 19.5 mg/dl vs. 140 ± 13.4 mg/dl; $P=.412$).

Outcome results values are reported in Tables 2 and 3.

4. Discussion

In this study, we investigated the prevalence of abnormal glucose metabolism by 2 h-OGTT and IR-index in patients with blepharoptosis of undetermined aetiology. Seventy-eight percent of our patients had IR, of whom following a 2 h-OGTT, the 34% having IGT, the 22% having DM and the 23% having only IR. These percentages were significantly higher than those reported in our control group ($P<.001$). Patients with IR are at high risk for developing DM [11]. Substantial clinical and experimental evidence suggest that both diabetes and IR cause endothelial dysfunctions [12]. Both IR and endothelial dysfunction appear to precede the development of overt hyperglycaemia in patients with type 2 diabetes. However, subsequent works emphasizing the microvascular and axonal injury of diabetic neuropathy and strict research criteria for diagnosis reinforced the popularly held notion that development of neuropathy required a prolonged period of hyperglycaemia [13]. A decade of small epidemiology studies provide evidence that early hyperglycaemia [6] or MS [7,14] is sufficient to damage distal peripheral nerves. In fact, the preponderance of clinical studies suggests that neuropathy is more common in patients with prediabetes, and that prediabetes is more common in patients with otherwise idiopathic neuropathy. As a matter of fact, a prospective study of 187 patients with otherwise idiopathic neuropathy finds 45% had IGT and an additional 15% had previously unrecognized diabetes [15]. Other studies, demonstrated neuropathologic changes in animal model that developed functional insulin-secreting tumours of the pancreas that temporally coincided with the onset of hyperinsulinemia [8,9]. A case-control study of 50 subjects with idiopathic neuropathy finds a prevalence of IGT or IFG nearly twice that of age-matched non-neuropathic control subjects, but after controlling for age and gender, this difference did not reach statistical significance. Besides the authors identified environmental toxic exposure and hypertriglyceridemia, but not glucose tolerance or IR as significant risk factors of chronic idiopathic polyneuropathy [16]. The relation between blepharoptosis and DM is well-known, conversely there are only some not controlled studies between blepharoptosis and manifestations of prediabetes [17,18]. Our data documented a strong linkage between blepharoptosis and glucose metabolism abnormality (IGT, DM, IR) in patients with normal fasting glycaemia. It is not surprising that IGT and IR would each confer increased risk for idiopathic blepharoptosis. The EuroDiab Study that followed 3000 subjects with type 1 diabetes for up to 7 years, found that among the 1200 subjects without neuropathy at baseline, hypertension, serum lipids and triglycerides, BMI, and smoking were each independently associated with increased risk of developing neuropathy at follow-up period [19]. We suggest that "idiopathic blephaptosis" is frequently a consequence of IR in the form of prediabetes. A methodological limitation to our study is the control group: to obtain a convenient sample of control subjects, we recruited people coming from the same geographic area as the patients, with similar dietary habits and life style, they were different from patients for age and sex. Nevertheless, after adjustment for these variables there was no difference in BMI, blood pressure, serum lipids, triglyceridemia and smoking use among normal and abnormal metabolism glucose patients and control subjects while the association between abnormal glucose metabolism and blepharoptosis remained strongly significant. Conversely, we found a close association between waist circumference and patients with idiopathic blepharoptosis ($P=.003$). Central adiposity in particular is closely associated with the development of IR [20]. These results were similar to previous studies [6,19]. Our data highlight IR as an independent risk factor for neuropathic injury. In fact, HOMA index value allowed more identification of a subgroup of patients (23%) with IR and NGM than in the controls ($P=.005$). In these patients the plasma glucose levels following the 2 h-OGTT test were within the normal range, whereas the plasma insulin levels and HOMA index values were markedly elevated (Glycaemia: 79.4 ± 9.3 mg/dl; Insulinemia: 48 ± 5.4 UI/ml; HOMA-index: 9.4 ± 1.4). Thus, we suggest an association between IR compensatory hyperinsulinemia, and idiopathic blephaptosis. In fact, IR leads to compensatory hyperinsulinism and subsequently, in the setting of physiologic euglycaemia, may have a role in slowing down or perhaps reversing the neuropathologic changes seen in these patients. This association, in our judgement, can be explained in several ways. First, the normality of glycaemic blood levels in idiopathic blepharoptosis group raises the hypothesis that neuropathic injury is not due to hyperglycaemia "*per se*" but to a common abnormality underlying the insulin metabolism. The second explanation would be related to effects of IR on endothelial dysfunction, induced by IR, not only linked to common pathogenetic mechanisms, involving deranged insulin signalling pathways, but also to other, indirect hormone action mechanisms [21]. Third, the microvascular dysfunction resulting from lipid deposition and oxidative stress to the vessel wall, may trigger an inflammatory reaction and the release of chemoattractans and cytokines worsens the IR and consequently endothelial dysfunction [22]. The microangiopaty may also be a compensatory response to endoneurial ischemia/hypoxia induced by chronic hyperinsulinemia [23]. Although our findings suggest that neuropathic injury is an early event in patients with glucose metabolism imbalance still not clinically manifested, nevertheless other causes of blepharoptosis than those investigated cannot be excluded. Finally, we propose that a 2 h-OGTT test and mainly HOMA-IR should be performed as a rule in all patients with idiopathic blepharoptosis, especially in the absence of other neurological signs. Our study could be criticized because the 2 h-OGTT was not performed after loading the diet with carbohydrates for 4 days, which is known to increase the proportion of patients in the IGT range [24]. This may represent a possible bias to our results. Nevertheless, the test was performed in the same way for patients and controls, so it is likely that the relative proportions of patients and controls in the IGT could remain unmodified.

Based on the results of this study, additional studies with age-matched case-control subjects are needed before definite causal relationships between blepharoptosis and prediabetes markers (IGT and/or IR) can be fully accepted.

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