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S100B as a glial cell marker in diabetic peripheral neuropathy

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HIGHLIGHTS

- We did not detect any concentration of GFAP in serum samples in both of the groups.
- Markedly decreased serum levels of S100B were obtained in diabetic patients.
- Serum S100B levels did not correlate with diabetic peripheral neuropathy in diabetics.

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ABSTRACT

Evidence suggests that acute and chronic hyperglycemia can cause oxidative stress in the peripheral nervous system which, in turn, can promote the development of diabetic neuropathy. Recent studies have found increased expression of glial fibrillary acidic protein (GFAP) and S100B, both of which are indicators of glial reactivity, in the neural and retinal tissues of diabetic rats. For the first time in the literature, the serum levels of GFAP and S100B were assessed in patients with diabetes to evaluate the potential of these factors to serve as peripheral glial biomarkers of diabetes and to investigate their relationship to diabetic peripheral neuropathy. This prospective clinical study included 72 patients with type 2 diabetes mellitus and 50 age- and sex-matched control subjects. All diabetic patients were assessed with respect to diabetes-related microvascular complications, such as peripheral neuropathy, retinopathy, and nephropathy. Serum samples were analyzed for human GFAP and S100B using a commercially available Enzyme-linked Immuno Sorbent Assay kit. GFAP was not detected in the serum samples of either diabetic or control patients ($p > 0.05$). However, we found a statistically significant decrease in S100B serum levels in patients with diabetes compared with control participants ($p < 0.001$). No associations between serum S100B levels and the presence of diabetic peripheral neuropathy or other microvascular complications were observed ($p > 0.05$). The findings of markedly decreased serum levels of S100B may possibly indicate a neuroprotective effect of S100B, whereas GFAP may be of no diagnostic value in human patients with diabetes.

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1. Introduction

Diabetes mellitus is the most common serious metabolic disorder in which microvascular complications, such as peripheral neuropathy, retinopathy, and nephropathy, regularly occur but may remain undetected in daily practice [12]. An easy and non-invasive screening test that can identify these types of complications would be of short-term and long-term benefit to patients with diabetes. This is particularly true in the case of peripheral neuropathy, which requires sensory and motor conduction studies on multiple nerves in the upper and lower limbs [17]. Needle examination and, rarely, sural and skin–punch biopsies are required for the diagnosis of a neuropathy when small fiber injury is the sole pathology and conduction studies are normal; however, these procedures are often painful to the patient [17].

Evidence suggests that acute and chronic hyperglycemia can cause oxidative stress in the peripheral nervous system (PNS)

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which, in turn, can promote the development of diabetic neuropathy [29]. Proteins damaged by oxidative stress exhibit decreased biological activity, which leads to reduced energy metabolism, decreased cell signaling and transport, and, ultimately, cell death [29]. Experimental animal and in vitro models of diabetes as well as clinical trials of antioxidants have strongly implicated hyperglycemia-induced oxidative stress in the manifestation of diabetic neuropathy [16,23,25]. Moreover, glial cells exhibit reactive gliosis, an early and obvious cellular response, following a variety of insults to the central nervous system (CNS; [4,6]). Glial cells play a vital role in the homeostatic regulation of the CNS as they are involved in neurotransmitter uptake, neuronal metabolic support, pH regulation, and neuronal survival against oxidative stress caused by free radicals [5,7]. Following hyperglycemia-induced oxidative or metabolic insults in the brain, astrocytes overexpress glial fibrillary acidic protein (GFAP) and S100B protein, both of which are indicators of glial reactivity [7]. Baydas et al. [5,8] recently found increased expression of GFAP and S100B in the neural and retinal tissues of diabetic rats. These authors suggested that the gliosis that accompanies diabetes occurs via free radical formation and that GFAP and S100B may be relevant markers of neurodegenerative changes in experimental models of diabetes [5,8]. Regarding clinical perspectives, these glial markers have been extensively studied in peripheral blood of patients with either traumatic brain injury [30] or cerebral infarcts [13] through the hypothesis of blood–brain barrier (BBB) permeability. Due primarily to the wide microcirculatory network, hyperglycemia-induced oxidative stress affects both central and peripheral organs, possibly resulting in overexpression of the glial biomarkers [29]. Then, we might expect that GFAP and S100B protein would be detected in the serum of individuals with diabetes, rather than being part of a mechanism regulating BBB permeability, in response to the excessive peripheral glial reactivity that accompanies diabetes. However, the level of glia in the serum samples of diabetic patients has yet to be investigated. Here, it is proposed that if hyperglycemia-induced oxidative stress were involved in the development of diabetic neuropathy, then peripheral glial markers, which represent diabetes-induced glial reactivity, may be a non-invasive assessment of peripheral neuropathy in diabetic patients. Thus, for the first time in the literature, the serum levels of GFAP and S100B were assessed in patients with diabetes to evaluate the potential of these factors to serve as peripheral glial biomarkers of diabetes and to investigate their relationship to diabetic peripheral neuropathy.

2. Material and methods

2.1. Study population

This prospective clinical study included 72 patients with type 2 diabetes mellitus and 50 age- and sex-matched control subjects ranging from 25 to 75 years of age. Type 2 diabetes mellitus was identified by the presence of fasting glucose levels ≥126 mg/dl or postprandial glucose levels ≥200 mg/dl concomitant with symptoms of diabetes or by treatment with insulin and/or oral hypoglycemic agents of previously diagnosed diabetes [1]. Patients with malignancy; chronic renal, hepatic, cardiovascular, or connective tissue diseases; thyroid disease; chronic obstructive pulmonary disease; history of local trauma or surgery; infections (Lyme disease, hepatitis, etc.); a vitamin-B12 deficiency; or a family history of neuropathy or a disease known to cause neuropathy were excluded from the study. Additionally, those who were pregnant, morbidly obese, current smokers, current consumers of alcohol, or users of drugs that cause neuropathy were also excluded from the subject pool. The study protocol was approved by the Bozok University Research Ethics Committee, and written informed consent was obtained from all participants.

Dependent variables included systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index (BMI), which was calculated as weight in kilograms divided by the square of height in meters [26]. Furthermore, fasting venous blood samples were taken from all subjects between 8:30 and 10:00 am, and routine hematological and biochemical analyses were performed by standard methods in our laboratory.

2.2. Assessment of peripheral neuropathy

All diabetic patients underwent conventional sensory and motor nerve conduction studies performed by the same neurologist, who was blind to the results. All nerve stimulations, including of the median, ulnar, deep peroneal, and tibial motor nerves and median, ulnar, and of the sural sensory nerves in both limbs, were performed with a Meledec Synergy electromyography (EMG) machine (Meledec Synergy; Oxford Instruments; Surrey, UK). Filter settings included a 20–2000 Hz bandpass for sensory nerve studies and a 2–10,000 Hz bandpass for motor nerve studies. The limb temperature of all subjects was maintained above 31–32 °C. Abnormal spontaneous activity, increased number of long-duration motor unit potentials, and decreased recruitment patterns were determined to be indicators of neuropathic changes. Based on EMG findings (nerve conduction velocity, amplitude, and distal latency) and a score of ≥4 on the Douleur Neuropathique 4 (DN4) questionnaire, peripheral neuropathy was confirmed or ruled out for each patient [9]. Of the diabetic patients, 37 (51.4%) were found to have peripheral neuropathy.

2.3. Assessment of retinopathy

Retinopathy status was assessed by fundoscopic eye examination performed by the same ophthalmologist who was blind to the status of the patients. Non-proliferative retinopathy was diagnosed according to the presence of cotton wool spots, micro-aneurysms, and/or boat-shaped hemorrhages during direct ophthalmoscopic examination. Proliferative retinopathy was diagnosed according to the presence of neovascularization in the retina [10]. Of the diabetic patients, 18 (25%) were found to have retinopathy; four patients exhibited the proliferative type, and the remainder exhibited the non-proliferative type.

2.4. Assessment of nephropathy

Nephropathy was diagnosed according to the presence of microalbuminuria, macroalbuminuria, or creatinine clearance of <90 mL/min. Microalbuminuria and macroalbuminuria were diagnosed based on the urinary albumin:creatinine ratio [10]: 30–300 mg albumin per gram of creatinine for microalbuminuria and >300 mg of albumin per gram of creatinine for macroalbuminuria. Three patients with diabetes were found to have nephropathy.

2.5. Biochemical analysis

Blood samples were collected in vacutainer tubes without anticoagulant supplements. All blood samples were centrifuged for 10 min at 3000 rpm, after which the supernatant was quickly removed and kept frozen at −80 °C until the assays were performed by an investigator blind to patient status. Serum samples were analyzed for human GFAP and S100B using a commercially available Enzyme-linked Immuno Sorbent Assay (ELISA) kit (human GFAP and S100B, BioVendor Research and Diagnostic Products; Heidelberg; Germany). The limits of detection for human GFAP and S100B were 0.045 ng/mL and 15 pg/mL, respectively. Serum GFAP concentrations were expressed as ng/mL, whereas S100B concentrations were expressed as pg/mL. The S100B levels of 98% of all subjects

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