ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.24179/kbbbbc.2022-89636

Increased C-Peptide and Insulin Resistance are Important in the Development of Paralysis in Patients with Idiopathic Peripheral Facial Paralysis

İdiyopatik Periferik Fasiyal Paraliziye Sahip Hastalarda Artmış C-Peptid ve İnsülin Rezistansı Paralizi Gelişiminde Önemlidir

Deniz AVCI[a], Abdullah EYVAZ[b]

[a]Clinic of Otorhinolaryngology, Head and Neck Surgery, Nevşehir State Hospital, Nevşehir, Türkiye
[b]Clinic of Internal Medicine, Nevşehir State Hospital, Nevşehir, Türkiye

This study was presented as an oral presentation at 42nd National Congress of Turkish Society of Otorhinolaryngology & Head and Neck Surgery, November 3-7, 2021, Kyrenia, Turkish Republic of Northern Cyprus.

ABSTRACT Objective: To investigate the possible predictive role of the effects of insulin resistance (IR), connecting peptide (C-peptide) and glucose metabolism on paralysis in patients with nondiabetic Bell's palsy (BP). **Material and Methods:** The prospective-controlled study included 40 patients (mean age 39.95±11.74 years) and 22 healthy volunteers (average age 36.95±9.8 years). Clinical severity of BP was assessed using the House-Brackmann Facial Nerve Grading System. In addition to routine examinations, glucose, insulin, hemoglobin A1c (HbA1c), HbA1c-Système International (HbA1c-SI), and C-peptide levels were measured after at least 8 hours of fasting. IR was evaluated using homeostatic model assessment for IR (HOMA-IR) at a cut-off value of 2.7. **Results:** Fasting glucose, fasting insulin, fasting C-peptide, HbA1c, HbA1c-SI, and HOMA-IR values were significantly higher in the BP group ($p<0.05$ for all). Additionally, all blood parameters were positively correlated and mean fasting insulin, fasting C-peptide, and HOMA-IR values were significantly correlated with each other. Mean HOMA-IR value was significantly higher in the BP group compared to the control group (4.2±2.39 vs. 2.61±1.13) ($p=0.004$). **Conclusion:** The significant increase in HOMA-IR values in BP patients suggests that IR is a facilitative risk factor for BP. In addition, we consider that there may be a strong relationship between BP and increased all values. We also propose that these values can be highly useful and indispensable parameters in the pathophysiology of BP, administration of prophylactic precautions for prediabetes.

Keywords: Bell's palsy; C-peptide; glucose; insulin resistance

ÖZET Amaç: Nondiyabetik idiyopatik periferik fasiyal paralizi [Bell's palsy (BP)] gelişen hastalarda insülin direnci [insulin resistance (IR)], bağlayıcı peptid [connecting peptide (C-peptid)] ve glukoz metabolizmasının paralizi gelişimi üzerine olası etkilerinin araştırılması amaçlandı. **Gereç ve Yöntemler:** Prospektif, kontrollü çalışmaya nondiyabetik 40 BP hastası (ortalama yaş 39,95±11,74) ve sağlıklı 22 gönüllü (ortalama yaş 36,95±9,8) alındı. BP derecesi "House-Brackmann Fasiyal Sinir Derecelendirme Sistemi" ile değerlendirildi. Hastaların rutin tetkikleri ile birlikte en az 8 saatlik açlık sonrası glukoz, insülin, hemoglobin A1c (HbA1c), "HbA1c-Système International (HbA1c-SI)" ve C-peptid seviyeleri ölçülerek değerlendirildi. IR'yi değerlendirmek için IR'nin homeostatik model değerlendirmesi [homeostatic model assessment (HOMA-IR)] >2,7 cut-off değeri göz önüne alınarak hesaplandı. **Bulgular:** Kontrol grubu ile kıyaslandığında açlık glukoz, açlık insülin, açlık C-peptid, HbA1c, HbA1c-SI ve HOMA-IR değerlerinin hepsi BP grubunda daha yüksek ve istatistiksel olarak daha anlamlı saptandı ($p<0,05$). Kan parametreleri birbirleri ile pozitif korelasyon gösterdi. Ortalama açlık insülini, açlık C-peptidi ve HOMA-IR değerleri birbirleriyle anlamlı şekilde ilişkiliydi. Ortalama HOMA-IR değeri BP grubunda kontrol grubuna göre anlamlı derecede yüksekti (sırasıyla 4,2±2,39, 2,61±1,13) ($p=0,004$). **Sonuç:** HOMA-IR değerlerinin BP hastalarında önemli ölçüde artması IR'nin BP için kolaylaştırıcı bir risk faktörü olduğunu gösterdi. Ayrıca artmış HOMA-IR, HbA1c, HbA1c-SI, C-peptid, açlık glukoz ve açlık insülin değerleri ile BP arasında güçlü bir patofizyolojik ilişki olabileceğini ve yine bu değerlerin prediyabet için profilaktik önlemlerin uygulanmasında oldukça yararlı ve vazgeçilmez parametreler olabileceğini düşünüyoruz.

Anahtar Kelimeler: Bell paralizi; C-peptid; glukoz; insülin rezistansı

Correspondence: Deniz AVCI
Clinic of Otorhinolaryngology, Head and Neck Surgery, Nevşehir State Hospital, Nevşehir, Türkiye
E-mail: deniz.avci@hotmail.com

Peer review under responsibility of Journal of Ear Nose Throat and Head Neck Surgery.

Received: 12 Mar 2022 ***Received in revised form:*** 05 May 2022 ***Accepted:*** 31 May 2022 ***Available online:*** 07 Jul 2022

The facial nerve (FN) consists of both motor and sensory components. Facial palsy (FP) is a neurological condition arising from partial or complete loss of the function of FN. FP can be idiopathic Bell's palsy (BP) or have a neurological, congenital, metabolic, infective, traumatic, iatrogenic, or neoplasia-related etiology. The incidence of FP varies between 17 and 35 per 100,000 population.[1] The incidence peaks between the ages of 15-45.[2] BP affects men and women equally and has been shown to have an increasing prevalence in pregnant women.[3]

Although BP, which causes cosmetic and functional deformity, is the most common cause of FP, a comprehensive assessment involving all differential diagnoses is critical for optimum management of patients due to the fact that better results can be obtained with prompt, accurate, and appropriate diagnosis and treatment.[1] The incidence and exact cause of BP are not fully understood and remain controversial. However, there is some evidence suggesting that latent herpes simplex virus Type 1 infection plays a role in its etiology.[4] It is considered that reactivation of this virus results in FN inflammation, thereby leading to reversible neuropraxia and ultimately to Wallerian degeneration.[3] Besides viral infection, vascular ischemia, autonomic dysregulation, and inflammation have also been associated with BP.[5]

In most patients with BP (85%), partial recovery occurs within 3-4 weeks and full recovery occurs within 6 months.[1] However, a small number of patients may have lifetime symptoms of BP and the disease may recur, though rarely.[6,7]

Systemic steroids are commonly used in the treatment of BP. However, corticosteroids have numerous side effects, with the most important one being hyperglycemia. Moreover, since there is no substantial evidence to show coexistence of diabetes mellitus (DM) or insulin or glucose metabolism dysfunction in BP patients, the use of steroids in BP patients remains controversial.[8] Nevertheless, we think that steroids can be safely used after the evaluation of patients for insulin resistance (IR), DM, and glucose metabolism, which will reduce the complication risk and will provide favorable outcomes by the use of effective treatment. Accordingly, the present study aimed to investigate the possible predictive and facilitating role of the effects of IR, connecting peptide (C-peptide) and glucose metabolism on the development of BP in patients with nondiabetic BP and to discuss the findings in line with the findings of rare studies in the literature.

MATERIAL AND METHODS

The prospective, observational and controlled clinical study included 40 nondiabetic BP patients (aged 19-68 years, mean age 39.95±11.74 years, 21 males and 19 females) and who presented to our ear, nose, and throat outpatient clinic with a diagnosis of BP between July 2020 and April 2021, and 22 healthy volunteers (aged 24-59 years, average age 36.95±9.8 years, 11 males and 11 females).

This study was accepted by Nevşehir Hacı Bektaş Veli University Scientific Research Ethics Committee (date: July 2, 2020; no: 2020.14.165) and this study was planned and performed in accordance with the Helsinki Declaration. Informed consent was obtained from the participants.

Inclusion criteria for the patients were as follows: absence of DM, normal body mass index (BMI), normal computed tomography (CT), physical examination, and audiometry findings, and no history of usage of steroids or other drugs. The control group included healthy individuals who had the same demographic and ethnic background and had similar dietary habits and lifestyles.

After an eight-hour fasting period, patients were evaluated for IR and glucose metabolism after a complete physical examination of the ear, nose, and throat prior to the initiation of the systemic steroid treatment in order to obtain a more accurate prognostic factor and IR.

In addition to routine examinations, glucose, insulin, hemoglobin A1c (HbA1c), HbA1c-Système International (HbA1c-SI), and C-peptide levels were measured after at least 8 hours of fasting. Homeostatic model assessment for IR (HOMA-IR) was calculated to evaluate IR using the following formula: basal plasma glucose (mg⁄dL) × basal plasma insulin (mU/L)⁄405.[9] In a similar way to the study by Bosco

et al., a HOMA-IR cut-off value of 2.7 was defined and thus the HOMA-IR values above 2.7 were accepted as IR-positive.[9] Demographic and clinical characteristics including age, gender, date of hospital admission, and affected side were recorded for each patient. Clinical severity of BP was evaluated using the House-Brackmann (HB) Facial Nerve Grading System.[10] HB stages of BP patients were divided into 2 groups as Stage 2-3 and Stage 4-5-6 groups, and a comparison was made between clinical parameters. Pure tone audiogram, cranial and temporal bone CT, and magnetic resonance imaging were performed to rule out other conditions that could have similar symptoms.

According to the World Health Organization, individuals with a BMI of ≥25 kg/m^2 are classified as overweight and those with a BMI of ≥30 kg/m^2 are classified as obese.[11] In our study, patients with a BMI of >25 kg/m^2 were excluded from the study. In addition, patients with any known external, middle and inner ear disease and history of surgery, peripheral FP secondary to surgery and trauma, herpes zoster oticus, hypertensive intracranial hemorrhage, DM, tumors of the cerebellopontine angle, a time from symptom onset to hospital admission of more than 10 days, uncontrolled systemic diseases, vascular ischemia, hyperlipidemia, malignancy, exposure to cold, acute and chronic inflammatory diseases, history of head trauma, hereditary or acquired hearing loss, congenital facial paralysis and a positive family history, pregnancy, autoimmune diseases, alcohol abuse, use of drugs that could affect glucose metabolism, and abnormal blood tests were excluded from the study.

STATISTICAL ANALYSIS

Data were analyzed using SPSS for Windows version 23.0 (Armonk, NY: IBM Corp.). Descriptives were stated as mean±standard deviation. Independent groups were compared using chi-square test. Normal distribution of continuous variables was assessed using Shapiro-Wilk test and Q-Q plots. Continuous variables with normal distribution were compared using independent samples t-test and those with non-normal distribution were compared using Mann-Whitney U test. Correlations between continuous variables were determined using Spearman's (for non-normally distributed variables) and Pearson's correlation (for normally distributed variables) analysis. A p value of <0.05 was considered significant.

RESULTS

In Table 1, the clinical and demographic data of the patients/groups are expressed.

The participants in the control group had no signs of BP, systemic disorders, DM, autoimmune and infectious conditions, and peripheral neuropathy. No significant difference was found between the 2 groups with regard to age, gender, and BMI values (p=0.31, p=0.34, and p=0.78, respectively). Present paralysis was the first attack of the patients. Most of the patients presented with left-sided BP. According to the HB Facial Nerve Grading System, the patients were mostly classified as Grade 3 and least commonly as Grade 4 and Grade 5 (Figure 1).

Time from symptom onset to hospital admission was 1 day in 15 (37.5%), 2 days in 15 (37.5%), 3 days in 8 (20%), 4 days in 1 (2.5%), and 7 days in 1 (2.5%) patient (mean, 2 days). All blood parameters were positively correlated with each other. Mean fasting insulin, fasting C-peptide, and HOMA-IR values were significantly correlated with each other.

The HB FN and grading system scores established a negative correlation only with HbA1c, HbA1c-SI, HOMA-IR and C-peptide values and this correlation was not significant with all blood parameters.

TABLE 1: Demographic and clinical characteristics of BP and control groups.

Variables	BP group (n=40)	Control group (n=22)
	Mean±SD	Mean±SD
Age, year	39.95±11.74	36.95±9.8
Male, n (%)	21(52.5%)	11(50%)
Female, n (%)	19(47.5%)	11(50%)
BMI, kg/m^2	22.49±1.82	22.35±1.84
Mean application time, day	2.0±1.15	
BP side, n (%)	Right	18(45%)
	Left	22(55%)

BP: Bell's palsy; SD: Standard deviation; BMI: Body mass index.

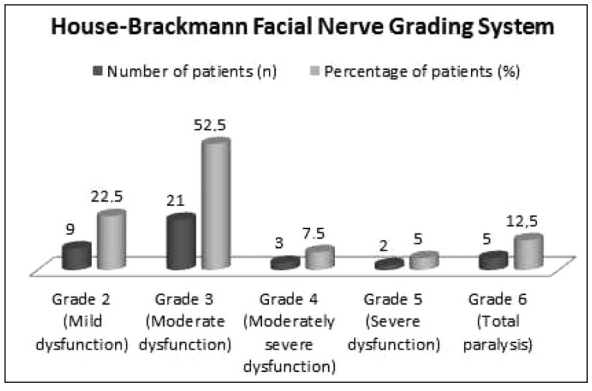

FIGURE 1: Distribution of patients according to House-Brackmann facial nerve grading system.

No more severe FN dysfunction was found in patients with higher HOMA-IR values. However, a positive correlation was found between age and all blood parameters and a significant correlation was found between age and fasting glucose values (Table 2).

Fasting glucose, fasting insulin, fasting C-peptide, HbA1c, HbA1c-SI, and HOMA-IR values were significantly higher in the BP group compared to the control group ($p<0.05$ for all) (Table 3) (Figure 2).

There was no significant difference between HB stages and clinical parameters. A comparison was made by dividing the HB stage into 2 groups as those with Stage 2-3 and those with Stage 4-5-6 (Table 4).

The HOMA-IR value was >2.7 in 28 (70%) of 40 BP patients and in 9 (40.9%) of 22 control subjects. The mean HOMA-IR value was significantly higher in the BP group compared to the control group (4.2±2.39 vs. 2.61±1.13) (p=0.004).

DISCUSSION

BP is the most common diagnosis associated with acute mononeuropathy as well as FN paralysis.[5] BP is a worrying health problem and has an extremely negative impact on both patients and their families. Early diagnosis and the determination of the cause of BP is highly important for developing and administering targeted treatment approaches. To this end, the present study reviewed the literature on the diagnosis of BP and investigated the possible pathophysiology of BP.

Due to its complex, osseous, and anatomical course, FN is the most susceptible nerve to ischemic and inflammatory events among all cranial nerves.[12] BP is considered to be associated with diabetic angiopathy and FN ischemia caused by the involvement of the vasa nervorum in many cases. A microvascular deficit in the vasa nervorum disrupts the nerve metabolism and leads to venous stasis, thereby resulting in the accumulation of toxic metabolites, edema, and ischemia.[13] Ischemia may be due to anatomical changes in the arterial wall, physical factors such as cold and pressure, vasoconstriction, and intravascular thrombosis. As a matter of fact, BP may most probably be the first sign of diabetic mononeuropathy. Therefore, glucose metabolism should be evaluated in every patient presenting with neurological deficits.[14,15] Microangiopathy may be a compensatory response to endoneurial ischemia/hypoxia caused by

TABLE 2: Correlations between age, gender and HB stages with clinic parameters.

	Age		Gender		HB stage	
Clinic parameters	**rho (ρ)**	**p**	**rho (ρ)**	**p**	**rho (ρ)**	**p**
Fasting insulin	0.05	0.699	0.295	0.02*	0.012	0.941
Hemoglobin A1c (%)	0.226	0.078	-0.174	0.17	-0.66	0.684
Hemoglobin A1c Système International	0.226	0.078	-0.174	0.177	-0.66	0.684
HOMA-IR	0.04	0.76	0.258	0.043*	-0.002	0.993
Fasting connecting peptide	0.204	0.112	0.302	0.017*	-0.024	0.882
	r	**p**	**r**	**p**	**r**	**p**
Fasting glucose	0.393	0.007*	-0.022	0.865	0.155	0.34

*p<0.05: Statistically significant; Spearman's (for non-normally distributed variables) and Pearson's correlation (for normally distributed variables) analysis were used; rho (ρ): Spearman correlation coefficient; r: Pearson's correlation coefficient; HB: House-Brackmann HOMA: Homeostatic model assessment; IR: Insulin resistance.

TABLE 3: Comparison of parameters of BP and control groups (Mann-Whitney U test, independent samples t-test and chi-square test were applied between groups).

Parameters	BP group (n=40) Mean±SD	Control group (n=22) Mean±SD	Reference values	p value
Fasting glucose	96.67±11.58	89.59±7.38	70-100 mg/dL	0.012*
Fasting insulin	18.01±9.9	11.91±5.37	2.6-24.9 mU/L	0.007*
Hemoglobin A1c (%)	5.9±0.61	5.26±0.21	4.5-6%	0.000*
Hemoglobin A1c Système International	37.5±3.67	34±2.33	25.7-42.1 mmol/mol	0.000*
HOMA-IR	4.2±2.39	2.61±1.13	>2.7 (cut-off value)	0.004*
Fasting connecting peptide	3.61±2.4	2.3±0.72	1.1-4.4 ng/mL	0.004*

*p<0.05: Statistically significant; BP: Bell's palsy; SD: Standard deviation; HOMA: Homeostatic model assessment; IR: Insulin resistance.

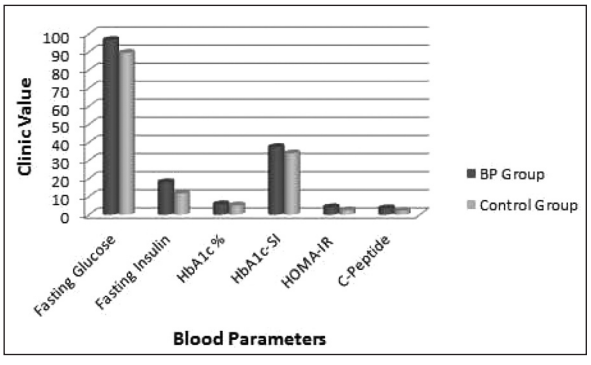

FIGURE 2: Graphical comparison of blood parameters of BP and control groups. BP: Bell's palsy; HbA1c: Hemoglobin A1c; HbA1c-SI: Hemoglobin A1c Systeme International; HOMA: Homeostatic model assessment; IR: Insulin resistance.

chronic hyperinsulinemia.[16] Moreover, various mechanisms such as hyperglycemia, increased oxidative stress, advanced glycation end product accumulation, axonal transport impairment, and impaired flow in the polyol pathway directly cause nerve damage.[17]

Individuals with BP often have a very good prognosis, but DM-related microangiopathy may be a prognostic and pathophysiological factor in BP.[18] Subclinical FN dysfunctions have been reported in 70% of patients with diabetic polyneuropathy. Early stages of hyperglycemia can cause distal nerve damage.[19] A prospective study evaluated 187 patients with idiopathic neuropathy and detected glucose metabolism dysfunction in 45% and detected undiagnosed DM in 15% of the patients. The authors also noted that the majority of BP patients had reduced glucose tolerance.[20]

There is no standard blood test to diagnose BP or predict its prognosis. Our hypothesis in this study was that IR or glucose metabolism dysfunction may play a role in the development of BP. Therefore, we did not include BP patients with abnormal fasting glucose levels in the study. After the completion of laboratory examinations, a combined therapy involving systemic steroids, gastroprotective agents, and ophtalmoprotective agents was administered in each patient. Nevertheless, no antiviral agents were used and no FN decompression or any other operation was administered in patients.

TABLE 4: Comparison of clinic parameters of Bell's palsy and HB stages (Mann-Whitney U test was used).

Parameters	HB stage (Stage 2 and 3) (n=30) Mean±SD	HB stage (Stage 4, 5 and 6) (n=10) Mean±SD	p value
Fasting glucose	95.83±12.45	99.2±8.46	0.425
Fasting insulin	17.8±8.72	18.66±13.37	0.779
Hemoglobin A1c (%)	5.92±0.7	5.82±0.19	0.836
Hemoglobin A1c Système International	41.28±7.71	40.12±2.12	0.836
HOMA-IR	4.05±2	4.64±3.39	0.901
Fasting connecting peptide	3.39±1.75	4.26±3.81	0.779

HB: House-Brackmann; SD: Standard deviation; HOMA: Homeostatic model assessment; IR: Insulin resistance.

In IR, body cells become resistant to the effects of insulin in the bloodstream. IR is defined as an impaired biologic response to insulin stimulation of target tissues, predominantly the liver, muscle, and adipose tissue. Therefore, the normal response to a certain amount of insulin is reduced. IR also leads to impaired glucose excretion, thereby producing a compensatory increase in hyperinsulinemia.[21-23] Clinical outcomes of IR include microvascular disease, retinopathy, nephropathy, peripheral neuropathy, hyperglycemia (Type 2 DM), hypertension, metabolic syndrome, dyslipidemia, increased levels of visceral adipose tissue, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and tendency for thrombosis.[24]

Since there is no generally accepted test for IR, the clinical definition of IR remains unclear.[25-27] The hyperinsulinemic-euglycemic glucose clamp technique is the gold standard for the measurement of IR, which is a research technique with limited clinical applicability. In contrast, HOMA-IR and HOMA2 are 2 IR measures that are based on fasting glucose and fasting insulin levels and are commonly used in clinical trials. Additionally, there are several clinically useful surrogate measures of IR, including the quantitative insulin-sensitivity check index, serum triglyceride, and the triglyceride/high-density lipoprotein ratio.[26]

HOMA is a widely used clinical method to evaluate beta-cell function and IR based on fasting glucose, insulin or C-peptide concentrations and can provide valuable data when used appropriately.[28] By comparison, HOMA-IR is a non-invasive and effective alternative IR measurement technique used for evaluating insulin sensitivity based on fasting glucose and serum insulin levels. Moreover, HOMA-IR is accepted as a standard technique for IR measurement in epidemiological studies.[29] For these reasons, we used HOMA-IR to evaluate IR in our study.

To our knowledge, there are very few controlled studies in the literature investigating the relationship between BP and IR. Karagöz et al. reported that IR was more common in nondiabetic BP patients.[30] However, as suggested by Karagöz et al., we also consider that calculating the HOMA-IR value can provide additional information for the prediction of the prognosis of BP.[30] In the present study, 70% of BP patients were accepted to have a higher HOMA-IR level based on the HOMA-IR cutoff value of 2.7 and the mean HOMA-IR value was found to be 4.2 in the BP group. These findings and the findings reported by Karagöz et al. suggest that IR may be an important risk factor and may have a key role in the etiopathogenesis of BP. Özer et al., in a similar way to our study, found a higher incidence of hyperglycemia and IR positivity and increased insulin values in most of their BP patients compared to the general population.[31] On the contrary, Bosco et al. reported that IR could not provide helpful information about BP when compared to the oral glucose tolerance test (OGTT) and also noted that IR led to an increased risk of BP in obese patients.[9] In the same study, a significant relationship was found between BP and glucose metabolism dysfunction after 2-hour OGTT in patients with normal fasting glycemia compared to the control group and the authors suggested that IR could be a risk factor for neuropathic damage due to BMI. Akintoye et al. emphasized that diabetic neuropathy is associated with increased IR. In our study, we think that FN neuropathy in non-diabetic patients may be related to IR.[32]

C-peptide is a measure of insulin secretion and can be used for demonstrating beta-cell function and can be used in HOMA modeling of IR. C-peptide provides a robust measure of insulin secretion but not a measure of insulin action.[28,33] C-peptide connects the alpha and beta chains of proinsulin and is mostly used for the differential diagnosis of fasting hypoglycemia and hyperinsulinism and for the measurement of insulin secretion reserve.[34] The normal physiological C-peptide plasma concentration in the fasting state is 0.9-1.8 ng/mL.[35] A high level of C-peptide can indicate IR, insulinoma, or kidney disease. The C-peptide level is typically low in Type 1 patients who cannot produce sufficient insulin.[34] C-peptide has also been shown to inhibit the formation of reactive oxygen species in various cell types, to inhibit the inflammatory pathway (anti-inflammatory effect), and to have cytoprotective and anti-apoptotic effects.[34,36,37] Accordingly, the higher and significant C-peptide levels in our BP group compared to the

control group implicates that BP develops due to an inflammatory process and also indicates the presence of IR in BP patients.

HbA1c, or glycated hemoglobin, measurements are an indicator of time-averaged glucose levels. HbA1c shows average blood glucose levels over the last 2-3 months due to the long lifespan of erythrocytes (about 120 days) and is used as the best marker of long-term DM control. The SI units are a true measure of HbA1c, eliminating possible confusion between HbA1c and glucose values.[38,39] For these reasons, in the present study, a true HbA1c measurement was obtained by using HbA1c-SI values. The American Diabetes Association defines prediabetes as HbA1c between 5.7-6.4%.[40] In our study, the mean HbA1c value was 5.9% in BP patients, which implicates that BP patients are prone to prediabetes.

The correlation between DM and BP was analyzed using HbA1c levels, not using fasting plasma glucose levels. A previous study found a significant positive correlation between the severity of BP and abnormal HbA1c values.[13] However, unlike that study, in our study, a non-significant negative correlation was found between HB grading and HbA1c and HbA1c-SI values. Another study also investigated HbA1c levels and found a significant relationship between increased HbA1c and slowed motor conduction velocity in large myelinated axons.[41]

Glycemic control plays a key role in the progression of neuropathy.[42] Therefore, targeted treatment of BP may involve the regulation of glucose metabolism even in nondiabetic IR patients.

The strength of our study was its prospective and controlled design. In addition, to our knowledge, there has been no study in the literature demonstrating the relationship between BP and both HbA1c-SI and C-peptide levels.

Nonetheless, this study was limited in several ways. First, no OGTT was performed due to the fact that it is a time-consuming, costly, and risky procedure and that there were only a few patients that consented to undergo OGTT. Second, the study had relatively a small number of patients mainly due to the low number of patients admitted to hospitals during the coronavirus disease-2019 pandemic. Finally, the effect of IR on the treatment and course of BP was not investigated.

Further large-scale studies comparing different measurement techniques and investigating the effect of etiologies of glucose metabolism dysfunction on BP with regard to patients' genders and genetic, racial, and environmental characteristics are needed to better elucidate the pathogenesis of IR and BP-related factors. We consider that once its mechanisms are fully elucidated by molecular studies, IR may be possible to prevent in the future with early diagnosis and lifestyle changes including diet change, regular exercise, and weight loss.

We think that the article deals with an important and multidisciplinary subject. Thus, the subject may be valuable. It concerns different professionals including internal medicine specialists and neurologists in academic environments.

CONCLUSION

Blood glucose and insulin metabolism parameters were higher in most patients with BP than in healthy volunteers. The significant increase in HOMA-IR values in BP patients suggests that IR is a facilitative risk factor for BP. In addition, we consider that there may be a strong relationship between BP and increased HOMA-IR, HbA1c, HbA1c-SI, C-peptide, fasting glucose, and fasting insulin values. We also propose that these values can be highly useful and indispensable parameters in the pathophysiology of BP, in the administration of prophylactic precautions for prediabetes

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Deniz Avcı;* ***Design:*** *Deniz Avcı, Abdullah Eyvaz;* ***Control/Supervision:*** *Deniz Avcı;* ***Data Collection and/or Processing:*** *Deniz Avcı, Abdullah Eyvaz;* ***Analysis and/or Interpretation:*** *Deniz Avcı;* ***Literature Review:*** *Deniz Avcı;* ***Writing the Article:*** *Deniz Avcı;* ***Critical Review:*** *Deniz Avcı;* ***References and Fundings:*** *Deniz Avcı;* ***Materials:*** *Deniz Avcı, Abdullah Eyvaz.*

REFEREENCES

1. Spencer CR, Irving RM. Causes and management of facial nerve palsy. Br J Hosp Med (Lond). 2016;77(12):686-91. [Crossref] [PubMed]
2. James DG. All that palsies is not Bell's. J R Soc Med. 1996;89(4):184-7. [Crossref] [PubMed] [PMC]
3. Holland NJ, Weiner GM. Recent developments in Bell's palsy. BMJ. 2004;329(7465):553-7. [Crossref] [PubMed] [PMC]
4. Finsterer J. Management of peripheral facial nerve palsy. Eur Arch Otorhinolaryngol. 2008;265(7):743-52. [Crossref] [PubMed] [PMC]
5. Monini S, Lazzarino AI, Iacolucci C, Buffoni A, Barbara M. Epidemiology of Bell's palsy in an Italian Health District: incidence and case-control study. Acta Otorhinolaryngol Ital. 2010;30(4):198. [PubMed] [PMC]
6. McCaul JA, Cascarini L, Godden D, Coombes D, Brennan PA, Kerawala CJ. Evidence based management of Bell's palsy. Br J Oral Maxillofac Surg. 2014;52(5):387-91. [Crossref] [PubMed]
7. Mooney T. Diagnosis and management of patients with Bell's palsy. Nurs Stand. 2013;28(14):44-9. [Crossref] [PubMed]
8. Dvorin EL, Ebell MH. Short-term systemic corticosteroids: appropriate use in primary care. Am Fam Physician. 2020;101(2):89-94. [PubMed]
9. Bosco D, Plastino M, Bosco F, Consoli A, Labate A, Pirritano D, et al. Bell's palsy: a manifestation of prediabetes? Acta Neurol Scand. 2011;123(1):68-72. [Crossref] [PubMed]
10. House JW, Brackmann DE. Facial nerve grading system. Otolaryngol Head Neck Surg. 1985;93(2):146-7. [Crossref] [PubMed]
11. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-63. Erratum in: Lancet. 2004;363(9412):902. [Crossref] [PubMed]
12. Mattox DE. Clinical disorders of the facial nerve. In: Flint PW, Haughey BH, Lund VJ, Niparko JK, Robbins KT, Thomas JR, Lesperance MM, eds. Cummings Otolaryngology: Head- Neck Surgery. 6th ed. Philadelphia, USA: Mosby Elsevier; 2015. p.2617-28. [Link]
13. Riga M, Kefalidis G, Danielides V. The role of diabetes mellitus in the clinical presentation and prognosis of Bell palsy. J Am Board Fam Med. 2012;25(6):819-26. [Crossref] [PubMed]
14. Zhang W, Xu L, Luo T, Wu F, Zhao B, Li X. The etiology of Bell's palsy: a review. J Neurol. 2020;267(7):1896-905. [Crossref] [PubMed] [PMC]
15. Korczyn AD. Bell's palsy and diabetes mellitus. Lancet. 1971;1(7690): 108-9. [Crossref] [PubMed]
16. Sugimoto K, Shoji M, Yasujima M, Suda T, Yagihashi S. Peripheral nerve endoneurial microangiopathy and necrosis in rats with insulinoma. Acta Neuropathol. 2004;108(6):503-14. [Crossref] [PubMed]
17. Singleton JR, Smith AG, Russell JW, Feldman EL. Microvascular complications of impaired glucose tolerance. Diabetes. 2003;52(12):2867-73. [Crossref] [PubMed]
18. Gilden DH. Clinical practice. Bell's Palsy. N Engl J Med. 2004;351(13):1323-31. [Crossref] [PubMed]
19. Smith AG, Singleton JR. Impaired glucose tolerance and neuropathy. Neurologist. 2008;14(1):23-9. [Crossref] [PubMed]
20. Smith AG, Singleton JR. The diagnostic yield of a standardized approach to idiopathic sensory-predominant neuropathy. Arch Intern Med. 2004;164(9):1021-5. [Crossref] [PubMed]
21. Seong J, Kang JY, Sun JS, Kim KW. Hypothalamic inflammation and obesity: a mechanistic review. Arch Pharm Res. 2019;42(5):383-92. [Crossref] [PubMed]
22. Brown JC, Harhay MO, Harhay MN. Anthropometrically predicted visceral adipose tissue and blood-based biomarkers: a cross-sectional analysis. Eur J Nutr. 2018;57(1):191-8. [Crossref] [PubMed] [PMC]
23. Deacon CF. Physiology and pharmacology of DPP-4 in glucose homeostasis and the treatment of type 2 diabetes. Front Endocrinol (Lausanne). 2019;10:80. Erratum in: Front Endocrinol (Lausanne). 2019;10:275. [Crossref] [PubMed] [PMC]
24. Kim B, Feldman EL. Insulin resistance in the nervous system. Trends Endocrinol Metab. 2012;23(3):133-41. [Crossref] [PubMed] [PMC]
25. Hossan T, Kundu S, Alam SS, Nagarajan S. Epigenetic modifications associated with the pathogenesis of type 2 diabetes mellitus. Endocr Metab Immune Disord Drug Targets. 2019;19(6):775-86. [Crossref] [PubMed]
26. Bothou C, Beuschlein F, Spyroglou A. Links between aldosterone excess and metabolic complications: A comprehensive review. Diabetes Metab. 2020;46(1):1-7. [Crossref] [PubMed]
27. Freeman AM, Pennings N. Insulin Resistance. 2021. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. [PubMed]
28. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27(6):1487-95. [Crossref] [PubMed]
29. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9. [Crossref] [PubMed]
30. Karagöz T, Bayir Ö, Çadalli Tatar E, Çakal E, Özdek A, Keseroğlu K, et al. Prognostic role of homeostasis model assessment and oral glucose tolerance test in nondiabetic patients with Bell's palsy. Turk J Med Sci. 2020;50(2):405-10. [Crossref] [PubMed] [PMC]
31. Özer G. The effect of insulin resistance on the House-Brackmann grade of facial paralysis in patients with Bell's palsy. J Surg Med. 2018;2(2):114-7. [Crossref]
32. Akintoye OO, Owoyele BV, Fabunmi OA, Raimi TH, Oniyide AA, Akintoye AO, et al. Diabetic neuropathy is associated with increased pain perception, low serum beta-endorphin and increase insulin resistance among Nigerian cohorts in Ekiti State. Heliyon. 2020;6(7):e04377. [Crossref] [PubMed] [PMC]
33. Leighton E, Sainsbury CA, Jones GC. A practical review of c-peptide testing in diabetes. Diabetes Ther. 2017;8(3):475-87. [Crossref] [PubMed] [PMC]
34. Venugopal SK, Mowery ML, Jialal I. C Peptide. 2020. In: StatPearls [Internet]. Treasure Island. (FL): StatPearls Publishing; 2021. [Link]
35. Yosten GL, Maric-Bilkan C, Luppi P, Wahren J. Physiological effects and therapeutic potential of proinsulin C-peptide. Am J Physiol Endocrinol Metab. 2014;307(11):E955-68. [Crossref] [PubMed] [PMC]
36. Bhatt MP, Lim YC, Kim YM, Ha KS. C-peptide activates AMPKα and prevents ROS-mediated mitochondrial fission and endothelial apoptosis in diabetes. Diabetes. 2013;62(11):3851-62. [Crossref] [PubMed] [PMC]
37. Luppi P, Cifarelli V, Tse H, Piganelli J, Trucco M. Human C-peptide antagonises high glucose-induced endothelial dysfunction through the nuclear factor-kappaB pathway. Diabetologia. 2008;51(8):1534-43. [Crossref] [PubMed]
38. Jones GR, Barker G, Goodall I, Schneider HG, Shephard MD, Twigg SM. Change of HbA1c reporting to the new SI units. Med J Aust. 2011;195(1):45-6. [Crossref] [PubMed]
39. Kahlon AS, Pathak R. Patterns of glycemic control using glycosylated hemoglobin in diabetics. J Pharm Bioallied Sci. 2011;3(3):324-8. [Crossref] [PubMed] [PMC]
40. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013;36 Suppl 1(Suppl 1):S67-74. [Crossref] [PubMed] [PMC]
41. Stino AM, Smith AG. Peripheral neuropathy in prediabetes and the metabolic syndrome. J Diabetes Investig. 2017;8(5):646-55. [Crossref] [PubMed] [PMC]
42. Feldman EL, Russell JW, Sullivan KA, Golovoy D. New insights into the pathogenesis of diabetic neuropathy. Curr Opin Neurol. 1999;12(5):553-63. [Crossref] [PubMed]