Glucose and Insulin Profiles and Their Correlations in Ménière’s Disease

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Abstract: Changes in carbohydrate metabolism, admittedly one of the most prevalent etiologies of Ménière’s syndrome, can be diagnosed early by 5-hour glucose and insulin curves with a 100-g glucose load, a test more sensitive than those traditionally used in investigating impaired glucose tolerance or diabetes mellitus. This study investigated carbohydrate metabolism characteristics in 64 patients with typical Ménière’s disease; We demonstrated that 72% of them had some variable degree of hyperinsulinemia as shown by their plasma insulin curves, whereas alterations on the glucose curve (reactive hypoglycemia or hyperglycemia) were found for only 21%. More advanced hyperinsulinemic conditions (i.e., glucose intolerance or diabetes mellitus) were usually associated with changes in lipid profiles and with a central pattern of fat distribution and systemic hypertension. We found a very strong correlation between insulin concentrations measured by chemoluminescence and by radioimmunoassay; the latter, however, showed values 1.3 times higher than those measured by chemoluminescence. These findings confirm the need to include 5-hour glucose and insulin curves in the diagnostic routine when investigating Ménière’s disease. In that way, an early diagnosis of hyperinsulinemia, the metabolic change most often involved in the pathogenesis of cochleovestibular disorders, can be made.

Key Words: endolymphatic hydrops; hyperinsulinemia; hypoglycemia; Ménière’s disease; prediabetic state

In 1972, the American Academy of Ophthalmology and Otolaryngology defined Ménière’s disease as a membranous labyrinth pathology characterized by deafness, vertigo, and tinnitus, and whose pathological substrate is the hydropic distension of the endolymphatic system [1-5]. Vestibular symptoms, auditory symptoms, and aural pressure, which occur simultaneously, define its characteristic clinical picture. Typical vestibular symptoms are paroxysmal episodes of vertigo, and auditory symptoms are sensorineural dysacusis and tinnitus [4,6-8].

Endolymphatic hydrops, found in histological studies of temporal bones, is the characteristic pathophysiological finding in Ménière’s disease, but a possible causal relationship between these two entities is still controversial. In fact, although all patients with clinically manifest Ménière’s disease (or syndrome) have endolymphatic hydrops, the converse is not true. Thus, some believe that other factors are directly or indirectly involved in this association and that endolymphatic hydrops is not the only entity responsible for the genesis of this pathology [4,9-13].

The significant participation of carbohydrate metabolism disorders in the genesis of cochleovestibular diseases is undeniable [14,15]. More than one-half of patients with Ménière’s syndrome have some degree of carbohydrate homeostasis dysfunction [16,17].

Carbohydrate dysmetabolic disorders are classified into four different clinical entities—each with its specific aspects concerning presentation, diagnosis, and management—that are in fact different stages of the same pathogenic process [18-21].

1. Hyperinsulinemia alone or hyperinsulinemia with euglycemia: This carbohydrate metabolism disorder, considered the earliest of those with potential clinical repercussions, appears to be associated al-
Glucose and Insulin Profiles as a possible diagnosis of insulin-reactive hypoglycemia. Glucose and insulin concentrations greater than glycemic values, with a difference exceeding renal threshold, attention should be paid not only to the known as patients is a direct consequence of a metabolic disorder. Patients between two consecutive samples, should be regarded as a possible diagnosis of insulin-reactive hypoglycemia diagnosed using a glucose curve.)

2. Hyperinsulinemia with reactive hypoglycemia [25-28].

3. Hyperinsulinemia with impaired glucose tolerance: an intermediate condition between the foregoing conditions and clinically manifest NIDDM [23]. Hyperinsulinemia alone may, and frequently does, develop into hyperinsulinemia with impaired glucose tolerance, even if the patient does not present with hypoglycemia directly.

4. Hyperinsulinemia with hyperglycemia: NIDDM, which has the highest potential for the involvement of key organs other than the inner ear, such as the kidneys, eyes, and cardiovascular system [23,24].

This sequence shows that hyperinsulinemia undoubtedly precedes hyperglycemia [29-32]. Hyperglycemia, especially fasting hyperglycemia, is thus a late marker of the complex process of metabolic disorders that has hyperinsulinemia as its earliest marker [19,33]. Hyperinsulinemia is believed to precede the development of NIDDM by some years and represents the extremes of the continuum of abnormal carbohydrate homeostasis. Hyperinsulinemia is thus the sine qua non condition for the development of NIDDM [19,22,34]. Hyperinsulinemic patients with a compromised inner ear frequently present with insulin-reactive hypoglycemia, usually because of an excessive production of insulin and not owing to a primary metabolic disorder [26,27].

The diagnostic criterion for insulin-reactive hyperglycemia has been the occurrence of at least one value equal to or less than 55 mg/dl [29]. What has been shown, however, is that in patients presenting with significant hyperglycemic peaks that exceed the 175-mg/dl renal threshold, attention should be paid not only to the individual glycemic values but to the rate of change. In these patients, a decline of greater than 1 mg/dl/min in glycemic values, with a difference exceeding 60 mg/dl between two consecutive samples, should be regarded as a possible diagnosis of insulin-reactive hyperglycemia [30].

The development of hyperinsulinemia in these patients is a direct consequence of a metabolic disorder known as insulin resistance, characterized by a reduced biological response to insulin at the cellular level. Patients with NIDDM show reductions in whole-body functional insulin concentrations greater than 35-40% [34-36].

Several authors [30,33] have shown that hyperinsulinemia is an earlier, more consistent change than hypoglycemia for the diagnosis of carbohydrate metabolism disorders because of the greater sensitivity of the insulin curve in comparison to the glucose curve. The main limitation of the use of the glucose curve in isolation is the possible occurrence of hypoglycemic peaks in the intervals between the collection of samples, which leads to false-negative results. Also known is that most hypoglycemic episodes occur more than 3 hours after the administration of oral glucose. This explains the low sensitivity of the traditional glucose tolerance test in the diagnosis of this condition: Only two samples are collected (fasting and 2 hours after the administration of a 75-mg glucose load) [30,33].

The different forms of carbohydrate metabolism disorders may affect the inner ear by means of basically the same pathogenic mechanisms, with a few specificities depending on the degree of metabolic disorder. NIDDM has the most pathogenic specificities for the inner ear and may cause a lesion there owing to mechanisms that are limited to this disorder [19,20].

Conditions associated with hyperinsulinemia lead to changes not only in glycemic levels but—apparently more important—in the sodium-potassium ATPase pump activity [37]. The persistence of this metabolic disorder results in injury to the outer hair cells and to the efferent pathways of the auditory system [38-41].

Hyperglycemic patients may develop cochleovestibular changes owing to three main mechanisms acting either alone or in association: neuropathy of the eighth cranial pair, vasculopathy of small vessels, and interference with the sodium-potassium ATPase pump activity in the inner ear, especially at the stria vascularis. The first two mechanisms are more relevant in patients who have severe diabetes mellitus (DM) that is difficult to manage; for these patients, such mechanisms are the main pathways of a cochleovestibular lesion [42-44].

The basic etiopathogenic characteristic of impaired glucose tolerance states and of the normoglycemic hyperinsulinemia states (occult DM) is interference in the sodium-potassium ATPase pump activity. Although these are milder forms of carbohydrate metabolism disorders, changes in the inner ear may occur because the sodium-potassium ATPase pump—the functioning of which changes in these patients—has one of the highest levels of activity in the stria vascularis. Consequently, cochleovestibular involvement may always be found, even at incipient stages of changes in glucose or insulin metabolism [38-40].

In patients with occult DM, the tests traditionally used to diagnose DM or impaired glucose tolerance usually yield normal results. Even the traditional glucose tolerance test with a 75-g glucose load has low diagnostic sensitivity. Therefore, the use of a variant of this tolerance test—the 5-hour glucose curve and the
simultaneous measurement of insulin concentrations—is advocated for the investigation of this pathological process [19,30,33].

The purpose of this study was to describe the glucose and insulin profiles of patients who had Ménière’s disease or syndrome and were seen in the otolaryngology outpatient clinic at Hospital de Clínicas de Porto Alegre from July 2001 to July 2003.

PATIENTS AND METHODS

We prospectively assessed all patients with a diagnosis of Ménière’s disease or syndrome seen in the outpatient clinic at Hospital de Clínicas de Porto Alegre from July 2001 to July 2003. We collected data about their otolaryngological history and examinations, degree of auditoryvestibular damage, and possible metabolic disorders. All patients underwent the following tests: pure-tone and speech audiometry, acoustic immittance measures, computed electroneystagmography, glycerol test, 5-hour glucose and insulin curves with a 100-g glucose load, glucose tolerance test (GTT) with a 75-g glucose load, and total serum cholesterol and serum triglycerides.

Patients included in the study had a syndromic diagnosis of typical Ménière’s disease. We used the following criteria, defined by the American Academy of Ophthalmology and Otolaryngology, to establish the syndromic diagnoses:

• Unilateral or bilateral floating sensorineural dysacusis demonstrated by serial audiometric studies or by a positive glycerol test result (or both)
• Recurring paroxysmal vertigo of the type found in Ménière’s disease (at least two episodes)
• Unilateral or bilateral tinnitus, depending on whether involvement was unilateral or bilateral

Exclusion criteria for our study were evidence of a compromised central nervous system (CNS) or of a tumor affecting cranial nerve VIII and evidence of other clinical entities that might justify the clinical picture (Ménière-like pathologies). We used magnetic resonance imaging to identify cranial nerve VIII lesions or involvement of the CNS in patients who presented with unilateral sensorineural dysacusis and whose brainstem audiometry results or other clinical data suggested retrocochlear involvement.

We collected data also about carbohydrate metabolism tests and other clinical or laboratory tests, directly or indirectly associated with glucose and insulin concentrations. We measured 2-hour GTT with a 75-g glucose load and plotted 5-hour glucose and insulin curves with a 100-g glucose load, measuring glucose concentrations using the enzymatic technique and insulin concentrations by means of radioimmunoassay (RIA) and chemoluminescence. We classified the insulin curves measured by RIA according to Kraft’s criteria: Type I, normal curve (fasting value = 0–25 μU/liter, peak [regardless of value] between 30 and 60 minutes, value at 120 min ≤ 50 μU/liter, sum of values at 120 and 180 min ≤ 60 μU/liter, values similar to fasting at 240–300 minutes); Type II (peak between 30 and 60 minutes, sum of values at 120 and 180 minutes between 60 and 100 μU/liter, or borderline); Type II (peak between 30 and 60 minutes, sum of values at 120 and 180 minutes ≥ 100 μU/liter); Type III (peak at 120 minutes); Type III (peak at 180 minutes); Type IV (fasting values ≥ 50 μU/liter); Type V (insulinopenia, all insulin values < 50 μU/liter).

The following criteria were adopted to diagnose DM: type IV insulin curve or fasting glycemia equal to or greater than 126 mg/dl on more than one occasion (adapted from the American Diabetes Association) or GTT with a 75-g glucose load with a 2-hour value equal to or greater than 200 mg/dl on more than one occasion (also adapted from the American Diabetes Association [20]).

The diagnostic criteria used to define impaired glucose tolerance (adapted from the American Diabetes Association) were fasting glycemia in excess of 110 mg/dl and lower than 126 mg/dl or GTT with a 75-g glucose load with a 2-hour value exceeding 140 mg/dl and lower than 200 mg/dl.

We defined hypoglycemia as one or more values equal to or less than 55 mg/dl at any point on the glucose curve or else a progression in the rate of glucose decline exceeding 1 mg/dl/min in patients with one or more glucose curve values of 175 mg/dl or more [29,30].

For total serum cholesterol, hypercholesterolemia was defined as total serum cholesterol concentrations of 240 mg/dl or more [45]. For serum triglycerides, hypertriglyceridemia was defined as serum triglyceride concentrations equal to or greater than 150 mg/dl [45].

We also measured waist-to-hip ratio and weight and height for all patients, who also answered questions about personal history of systemic hypertension (SHT). The central pattern of fat distribution was defined as a BMI of 25–29 kg/m 2 or more [45]. For serum triglycerides, hypertriglyceridemia was defined as serum triglyceride concentrations equal to or greater than 150 mg/dl [45].

RESULTS

Sixty-four patients were included in this study: 36 women (56.25%) and 28 men (43.75%). Patients’ mean
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Figure 1. Distribution of patients according to stage of hearing loss.

Age was 47.8 years; standard deviation (SD) was 3.2 years. Thirty patients (46.87%) presented with bilateral cochleovestibular damage. The mean time of progression of symptoms was 12.5 years (SD, 1.8 years).

Data on hearing loss, calculated as the mean value of hearing thresholds from 500 to 3,000 Hz in the diseased ear or in the ear that had the greater damage (unilateral or bilateral disease, respectively) are shown in Figure 1. The insulin curve for 50 patients (78.12%) showed abnormal values (Table 1). Table 1 shows that type II (39.06%) and type II A (18.75%) insulin curves (Kraft criteria) were the most frequent types.

Hypoglycemia on the glucose curve was found for only 10 (15.62%) of the 64 patients: 8 received diagnoses of hypoglycemia owing to one or more values of 55 mg/dl or less on the glucose curve, and 2 owing to a progression in the rate of glucose decline exceeding 1 mg/dl/min.

Fifteen patients (23.43%) had total serum cholesterol concentrations above the normal limit. Five patients (7.81%) had abnormal serum triglyceride concentrations. Twenty-four patients (37.5%) were overweight, and 10 (15.62%) were obese. Thirty patients (46.87%) had a central pattern of fat distribution.

Table 2 shows the degree of correlation between some of the variables studied and the sum of insulin concentrations on the insulin curve measured by RIA during the second and third hours. The table also shows statistically significant positive correlations between the sum of insulin concentrations at 120 and 180 minutes and BMI and waist-to-hip ratio. The correlation of insulin concentrations with BMI is moderate ($r$ between 0.3 and 0.6) and strong with waist-to-hip ratio ($r$ between 0.6 and 0.9). No statistically significant correlation was found between insulin concentrations at 120 and 180 minutes and total cholesterol or serum triglycerides.

The comparison between mean insulin values at different points on the curve measured by means of RIA and chemoluminescence revealed a strong, statistically significant positive correlation ($r = 0.9; p < .0001$) between these two methods. Chemoluminescence results were, however, almost 1.3 times lower than those obtained by RIA ($p < .05$).

Of the 46 patients diagnosed as hyperinsulinemic, 4 also met diagnostic criteria for impaired glucose tolerance, as did 3 for NIDDM. The distribution of the population studied according to the four possible types of carbohydrate metabolism disorders is shown in Table 3.

Table 2. Degree of Correlation Between Some of the Variables Studied and the Sum of Insulin Concentrations

<table>
<thead>
<tr>
<th>Variable</th>
<th>$r$</th>
<th>Level of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.4</td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.7</td>
<td>$p &lt; .001$</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.5</td>
<td>$p &lt; .05$</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.3</td>
<td>$p &gt; .20$</td>
</tr>
</tbody>
</table>

BMI = body mass index.

a progression in the rate of glucose decline exceeding 1 mg/dl/min.

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Table 3. Types of Carbohydrate Metabolism Disorders in Patients with Ménière's Disease

<table>
<thead>
<tr>
<th>Type of Impairment</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperinsulinemia with euglycemia</td>
<td>29 (45%)</td>
</tr>
<tr>
<td>Hyperinsulinemia with reactive hypoglycemia</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>Hyperinsulinemia with glucose intolerance</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Hyperinsulinemia with hyperglycemia (NIDDM)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

NIDDM = non-insulin-dependent diabetes mellitus.
The chi-square test was used to evaluate the correlation between carbohydrate metabolism disorders and hypercholesterolemia. Results revealed that patients with Ménière's syndrome and carbohydrate metabolism disorders are more often hypercholesterolemic than are those with Ménière's disease but no carbohydrate metabolism disorders ($p < .001$).

The analysis of adjusted residuals revealed that hypercholesterolemia was found significantly more frequently in hyperinsulinemic patients with impaired glucose tolerance and in those with hyperglycemia ($p_{R^2} < 0.05$). The same analysis of residuals did not reveal any statistically significant association between hyperinsulinemia with euglycemia or reactive hypoglycemia and hypercholesterolemia in this population of patients with Ménière's disease. No statistically significant association was found between carbohydrate metabolism disorders and hypertriglyceridemia.

The chi-square test results also showed a statistically significant association between carbohydrate metabolism disorders and obesity ($0.05 > p > .01$). The analysis of residuals revealed a statistically significant association of obesity and forms of hyperinsulinemia with impaired glucose tolerance and hyperglycemia. The other forms of hyperinsulinemia did not show any statistically significant association with obesity.

The association between carbohydrate metabolism disorders and a central pattern of fat distribution in patients with Ménière's disease was also statistically significant ($p < .0001$). As with obesity, the analysis of adjusted residuals showed a statistically significant association only between the central pattern of fat distribution and the carbohydrate metabolism disorders characterized by hyperinsulinemia with impaired glucose tolerance or by hyperinsulinemia with hyperglycemia (NIDDM).

Moreover, chi-square test results revealed a statistically significant association ($p < .001$) between carbohydrate metabolism disorders and SHT. Here, once again, the analysis of residuals revealed a statistically significant association only between SHT and the hyperinsulinemic forms of impaired glucose tolerance and NIDDM.

**DISCUSSION**

The demonstration that so-called occult diabetes precedes the development of impaired glucose tolerance and NIDDM has led researchers to assign a progressively higher value to hyperinsulinemia as a key metabolic change to be investigated when occult diabetes is suspected. In fact, the progressive rise in insulin concentrations is known to occur long before any change can be observed in glycemic levels measured by means of fasting glyceemia, GTT, or even glucose curves.

In this study, the insulin curves for approximately 71.87% of the patients (n = 46) with Ménière's disease revealed hyperinsulinemia, whereas GTT results compatible with impaired glucose tolerance were found for only 6.25% (4 patients), and changes in fasting glyceemia or GTT (or both) suggesting NIDDM were seen for only 4.69% (3 patients). Even when the results of the glucose curves were taken into account, results indicating reactive hypoglycemia were found for only 15.62% of the patients (10 patients). These results demonstrate that the insulin curve has significantly higher sensitivity than any other single diagnostic test in diagnosing carbohydrate metabolism disorders.

We used the chi-square test to evaluate the statistical significance of the different types of insulin curves observed in this population. The finding of a chi-square value with a level of significance between 0.01 and 0.02 demonstrates that it is highly unlikely that the observed distribution of the different types of insulin curve were obtained by chance.

The analysis of the adjusted residuals, combined with the percentages shown in Table 1, demonstrated that the frequency of curves II to V in the population studied was significantly higher than would be expected if no association existed between these types of insulin curve and Ménière's disease. In this study, we found a close correlation between insulin concentrations measured by RIA and by chemoluminescence, but results yielded by chemoluminescence were approximately 1.3 times lower. This is accounted for by the fact that, together with insulin, the RIA technique also measures proinsulin and some of its metabolites in such a manner that it actually overestimates insulin values [37].

The demonstration of a statistically significant positive correlation for patients with Ménière's disease in more advanced hyperinsulinemic states (i.e., impaired glucose tolerance and NIDDM) and the variables obesity, total cholesterol, SHT, and central pattern of fat distribution is in agreement with the syndrome X concept, which relates peripheral insulin resistance, which is characteristic of hyperinsulinemic states, to SHT and to hyperlipidemia [46,47].

According to several authors, the simultaneous occurrence of known risk factors for atherosclerotic disease may result from a genetic defect, constituting what is called syndrome X or insulin resistance syndrome. The latter, in which insulin resistance is the key alteration, is characterized by the simultaneous occurrence of hyperglycemia, hyperinsulinemia, hyperlipidemia, and SHT. Peripheral insulin resistance is believed to lead to hyperinsulinemia, which in turn may or may not be able to correct hyperglycemia. Also, hyperinsulinemia is believed to result in increased very-low-density lipoprotein production in the liver (dyslipidemia), and
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high insulin concentrations are thought to cause endothelial proliferation that promotes atherosclerosis. Although such associations have been well established, the precise mechanism of their interrelationship remains a matter of speculation. Patients with these characteristics, similarly to other subgroups of patients with carbohydrate metabolism disorders, may develop cochleovestibular signs and symptoms that often constitute the initial form of presentation of the disease [46,47].

The results of this study suggest the need to evaluate systematically the rate of glucose decline in patients whose concentrations are higher than the renal threshold of 175 mg/dl at one or more points on the glucose curve. Although this study has not revealed any statistically significant correlation between hyperinsulinemia and total serum cholesterol, we did find a statistically significant association between hypercholesterolemia and more severe hyperinsulinemic states, such as impaired glucose tolerance and NIDDM, in patients with Ménière's disease. These findings suggest that the changes in cholesterol concentrations in these patients are associated with more severe or more lasting dysmetabolic states, in which the change in cholesterol concentrations could be a possible etiopathogenic factor in persistent hyperinsulinemia.

Similarly to those demonstrated for total cholesterol concentrations, the results of this study showed a statistically significant association between obesity and dysmetabolic states in cases of impaired glucose tolerance and NIDDM but not in cases of euglycemic hyperinsulinemia or in reactive hypoglycemia. We found similar associations for central patterns of fat distribution and SHT. A joint analysis of these results suggests that the initial hyperinsulinemic states (i.e., those accompanied by euglycemia or reactive hypoglycemia) are not, as a rule, associated with plurimetabolic disorders and that they therefore exist as single metabolic changes.

The development of impaired glucose tolerance thus appears to be the point from which other metabolic changes—above all, those affecting lipid profiles and fat distribution patterns—become more prevalent. Whether these characteristics coexist only as independent alterations or whether they bear a causal relationship to each other cannot thus far be said. However, of the changes in carbohydrate metabolism profile, the stages of impaired glucose tolerance and, more important, of NIDDM are closely correlated with those measured by RIA but are approximately 1.3 times lower.

CONCLUSIONS

The results of this study confirm the significant percentage of patients with a syndromic diagnosis of Ménière's disease and changes in carbohydrate metabolism, most of them diagnosed only by 5-hour insulin curves. For patients with one or more values equal to or greater than 175 mg/dl on the glucose curve, the measurement of the rate of glucose decline is the most sensitive method to diagnose reactive hypoglycemia. Patients with Ménière's syndrome associated with impaired glucose tolerance or NIDDM have hypercholesterolemia, obesity, a central pattern of fat distribution, and SHT more frequently than do those who have Ménière’s syndrome associated with less severe hyperinsulinemic states. Insulin concentrations measured by chemoluminescence are closely correlated with those measured by RIA but are approximately 1.3 times lower.

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