weeks after discontinuing valproate is shown in Figure 1C and D. Her CST score became normal (20/20).

With hindsight, several hypotheses might explain the dramatic effects of valproate. First, valproate has high protein binding, more than 80%, mainly to albumin. Only free drug can cross the plasma membrane and bind with the receptor for pharmacological action. Free valproate concentrations mirror cerebral spinal fluid concentration. Valproate has a narrow therapeutic index, and toxicity may be encountered slightly above the upper end of the therapeutic range. For instance, a lowering of serum albumin from 40 to 30 g/L may double the amount of free valproate.[9] In this patient, serum albumin was 24 g/L. Second, in renal failure, unknown compounds displace valproate from protein-binding sites and may increase the free fraction up to 20% to 30% (normally 10%).[9] This patient had a toxic free fraction and concentration in the serum of 24% and 11 mg/L (normal range 5–10 mg/L) and liquor of 22% and 10 mg/L (normal range 5–10 mg/L). Third, mycophenolate is also a strongly protein-bound drug (92–98%) and may have further increased the free valproate level. Finally, this patient had an intermediate-metabolizer (CYP2C9*3) heterozygous genotype, which can also lead to a higher free valproate level.[9]

It was concluded that valproate intoxication caused by a too-high (toxic) free concentration could entirely explain the RPD. The subtherapeutic total serum valproate level was initially misleading. Neurotoxicity has been described only in patients with normal or high total levels of valproate.[4–8]

Conditions such as hypoalbuminemia and renal failure can lead to a significant increase in free concentrations, resulting in (neuro)toxicity even if the total valproate level is within or below therapeutic range. In patients with renal failure, hypoalbuminemia, or prescription of highly protein bound medication, monitoring of free valproate concentration is recommended. Free drug concentration of valproate is easily measured in clinical laboratories, and this method is widely available.

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INSOMNIA INCREASES INSULIN RESISTANCE AND INSULIN SECRETION IN ELDERLY PEOPLE

To the Editor: Elderly people with insomnia showed high insulin resistance and high insulin secretion after an oral glucose tolerance test (OGTT). Decreased insulin secretion is not a cause of diabets but rather a consequence of insulin resistance in elderly people with insomnia.

Aging is common factor known to contribute to the development of diabetes mellitus[1] and insomnia.[2] Difficulties initiating and maintaining sleep are associated with diabetes

mellitus,[3] and diabetes mellitus itself can impair the quantity and quality of sleep conversely.[4] Although diabetes mellitus and insomnia are closely correlated with one another, it is controversial whether low insulin secretion or high insulin resistance more strongly influences the beginning of diabetes mellitus in elderly people with insomnia. The OGTT is the most sensitive measure of glycemic status, but no data exist to evaluate glycemic status using OGTT in elderly people with and without insomnia. To clarify the relationship between insomnia and glucose tolerance, the 75-g OGTT was used to evaluate elderly people with and without insomnia.

METHODS

In August 2006 and 2007 at the healthcare center of Tosa Town, 402 subjects aged 75 and older were recruited. Written informed consent for participation in the study was obtained from participants. Participants were divided into three groups according to the Japanese Society of Sleep Research definition and frequency of hypnotic drug use. Insomnia was defined as a complaint of insomnia with duration of at least 3 months, with hypnotic drugs used almost every day. Poor sleep was defined as a moderate to severe complaint of difficulty falling asleep, difficulty staying asleep, early final awaking, or unrefreshing sleep and occasional use of hypnotic drugs. Normal sleep was defined as the absence of any symptom and non-use of hypnotic drugs. Glycemic status was evaluated using the 75-g OGTT, and the functions of insulin resistance and insulin secretion were calculated using the following equations: homeostatic model assessment (HOMA)-R = fasting plasma glucose (mg/dL) × fasting plasma insulin (μU/mL)/405; HOMA-β = fasting plasma insulin (μU/mL) × 360/(fasting plasma glucose (mg/dL) − 63). The insulin increase occurring after OGTT was calculated as a marker of insulin secretion.

Statistical Analysis

Paired *t*-tests and analyses of variance were used for analyses (JMP, SAS Institute, Inc., Cary, NC). Variables are presented as means with 95% confidence intervals (CIs). $P < .05$ was considered statistically significant.

RESULTS

Subject characteristics are presented in Table 1. The mean age was 73.8. Female participants constituted 63.0% of the sample and had a higher prevalence of poor sleep. Body weight, body mass index, waist measurements, and fasting plasma glucose were not different between the three groups, although mean glucose concentration after OGTT (insomnia: 153.4 mg/dL, 95% CI = 134.6–172.1; poor sleep: 145.4 mg/dL, 95% CI = 134.0–156.9; normal sleep: 141.5 mg/dL, 95% CI = 135.0–147.9, $P = .009$) was significantly higher in the insomnia group than in the other groups. Insulin before OGTT (insomnia: 8.2 μU/mL, 95% CI = 6.9–9.4; poor sleep: 5.4 μU/mL, 95% CI = 4.7–6.2; normal sleep: 5.1 μU/mL, 95% CI = 4.7–5.6), insulin after OGTT (insomnia: 67.9 μU/mL, 95% CI = 55.2–80.5; poor sleep: 43.7 μU/mL, 95% CI = 36.0–51.4; normal sleep: 42.6 μU/mL, 95% CI = 38.2–46.9), and insulin secretion according to OGTT (insomnia: 59.7 μU/mL, 95% CI = 47.6–71.8; poor sleep: 38.3 μU/mL, 95% CI = 30.9–45.7; normal sleep: 37.4 μU/mL, 95% CI = 33.3–41.6, $P < .001$) were all significantly higher in the insomnia group. Insulin secretion after OGTT was significantly higher in the insomnia group. HOMA-R (insomnia: 2.11, 95% CI = 1.76–2.46; poor sleep: 1.34, 95% CI = 1.13–1.55; normal sleep: 1.26, 95% CI = 1.14–1.38) and HOMA-β (insomnia: 83.4, 95% CI = 69.9–96.1; poor sleep: 60.2, 95% CI = 52.1–68.0; normal sleep: 57.6, 95% CI = 53.2–62.0, $P < .001$) were significantly higher in the insomnia group. Data for glycosylated hemoglobin were not different between the three groups.

DISCUSSION

The main finding of this study was that insomnia was associated with high insulin resistance and high insulin secretion. Sleep disturbances induced insulin resistance through several potential mechanisms, including sympathetic overactivity[5] and altered secretion of counterregulatory hormones during sleep.[6] Sympathetic overactivity and high counterregulatory hormones during sleep induced insulin resistance and thereby caused hyperinsulinemia in the morning.[7] Therefore, the insulin increase after glucose loading shown in these results probably occurred to compensate for low insulin action caused by insulin resistance. A previous study reported that restricted sleeping induced high fasting plasma glucose and low insulin secretion.[8,9] These results appear to conflict with those reported herein, although insulin secretion was estimated according to intravenous glucose infusion in the earlier study. The current study investigated insulin secretion using OGTT, involving incretin effects, which engenders enhanced insulin secretion after oral glucose loading.[10] Differences between these data and the data from the previous study might be attributable to incretin effects. The data from the current study indicate that elderly people with insomnia might have greater insulin resistance but that insulin secretion is prevented through incretin effects. In conclusion, insulin resistance is more influential than low insulin secretion on the glycemic status of elderly people with insomnia.

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Table 1. Characteristics of the Three Groups

Value	All (N = 404)	Insomnia (n = 33)	Poor Sleep (n = 89)	Normal Sleep (n = 282)	*P*-Value
Age, mean (95% CI)	73.8 (72.8–74.8)	74.6 (71.2–78.6)	76.6 (74.5–78.6)	73.3 (72.1–74.4)	.05
Female, %	63.0	63.6	73.0*	58.9	.02
Weight, kg, mean (95% CI)	53.1 (52.1–54.0)	54.8 (51.4–58.1)	51.2 (49.2–53.2)	53.4 (52.3–54.5)	.41
Body mass index, kg/m^2, mean (95% CI)	23.1 (22.8–23.4)	23.8 (22.7–24.9)	22.9 (22.3–23.6)	23.1 (22.8–23.5)	.40
Waist circumference, cm, mean (95% CI)	82.7 (81.8–83.6)	84.4 (81.2–87.8)	80.9 (78.9–83.0)	83.1 (82.1–84.2)	.10
Mini-Mental State Examination score, points, mean (95% CI)	25.8 (25.2–26.3)	25.4 (23.6–27.2)	26.4 (25.5–27.5)	25.5 (24.8–26.2)	.25
Timed Up and Go, s, mean (95% CI)	13.7 (13.2–14.3)	14.5 (12.8–16.3)	14.2 (13.1–15.3)	13.4 (12.8–14.1)	.30
Daily alcohol use, %	19.3	15.2	11.2	22.3	.06
Current smoking, %	6.9	0.0*	1.1*	9.6	.03
Hypertension, %	33.0	51.5	45.2	43.5	.18
Dyslipidemia, %	42.8	41.4	40.5	30.4	.15
Cardiovascular disease, %	12.4	12.1	10.1	12.8	.58
Stroke, %	12.1	21.2	9.0	12.4	.29
Double question positive, %	38.1	60.6*	47.2	32.6	<.001
Systolic blood pressure, mmHg, mean (95% CI)	129.6 (127.5–131.8)	136.4 (131.8–141.0)*	132.1 (124.2–140.0)	127.4 (124.8–130.0)	.03
Diastolic blood pressure, mmHg, mean (95% CI)	73.8 (72.5–75.0)	78.3 (73.9–82.6)*	75.2 (72.7–77.8)	72.8 (71.4–74.2)	.03
Plasma glucose, mg/dL, mean (95% CI)					
Before OGTT	96.8 (95.5–98.1)	100.4 (95.8–104.9)	97.0 (94.3–99.8)	96.5 (95.0–98.1)	.28
After OGTT	142.7 (137.5–148.0)	153.4 (134.6–172.1)*	145.4 (134.0–156.9)	141.5 (135.0–147.9)	.009
Immunoreactive insulin, μU/mL, mean (95% CI)					
Before	5.4 (5.0–5.8)	8.2 (6.9–9.4)*	5.4 (4/7–6.2)	5.1 (4.7–5.6)	<.001
After	44.9 (41.3–48.5)	67.9 (55.2–80.5)*	43.7 (36.0–51.4)	42.6 (38.2–46.9)	<.001
Homeostatic model assessment, mean (95% CI)					
Insulin resistance	1.33 (1.23–1.43)	2.11 (1.76–2.46)*	1.34 (1.13–1.55)	1.26 (1.14–1.38)	<.001
Beta cell function	59.9 (56.2–63.6)	83.4 (69.9–96.1)*	60.2 (52.1–68.0)	57.6 (53.2–62.0)	.002
Immunoreactive insulin secretion, μU/mL, mean (95% CI)	39.5 (36.1–42.9)	59.7 (47.6–71.8)*	38.3 (30.9–45.7)	37.4 (33.3–41.6)	<.001
Glycosylated hemoglobin, %, mean (95% CI)	5.4 (5.4–5.4)	5.4 (5.2–5.6)	5.4 (5.3–5.6)	5.4 (5.4–5.5)	.77
Albumin, mg/dL, mean (95% CI)	4.4 (4.3–4.4)	4.4 (4.3–4.5)	4.3 (4.3–4.4)	4.4 (4.3–4.4)	.13
Low-density lipoprotein cholesterol, mg/dL, mean (95% CI)	122.8 (119.8–126.0)	128.5 (117.4–139.7)	124.2 (117.6–131.0)	121.8 (118.1–125.5)	.47
triglycerides, mg/dL, mean (95% CI)	102.8 (97.9–107.8)	125.7 (108.0–143.5)*	104.0 (93.4–114.6)	100.0 (94.2–105.6)	.03
high-density lipoprotein cholesterol, mg/dL, mean (95% CI)	56.3 (54.8–57.9)	52.4 (46.9–57.9)	54.3 (51.0–57.5)	57.4 (55.6–59.2)	.08
Uric acid, mg/dL, mean (95% CI)	5.6 (5.4–5.7)	6.0 (5.5–6.5)	5.4 (5.1–5.7)	5.6 (5.4–5.7)	.09

*Versus other two groups; <.05.
CI = confidence interval; OGTT = oral glucose tolerance test.

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TOOTH LOSS AND DENTAL HEALTHCARE COVERAGE IN OLDER RURAL MEXICAN ADULTS LIVING IN POVERTY

To the Editor: Oral diseases, according to the 2003 World Oral Health Report, are a significant public health problem worldwide, and their effect on individuals and communities are of great importance.[1] It has been estimated that edentulism caused a total of 2,747 thousands of disability adjusted life years lost in 2001 worldwide, of which 55% were in women.[2] The fact that low- and middle-income countries accounted for 84% of the global burden of this condition highlights inequalities across countries.[2] The World Health Organization considers edentulism to be a poor public health outcome that substantially affects oral and general health status, as well as health-related quality of life. Recent reports place Mexico among countries with high prevalence of edentulism for people aged 65 and older.[3,4] This condition is found to be associated with sex (more common in women), poverty, and individual behavior (smoking).[4] The cumulative effects of dental caries and periodontal diseases, as well as treatment decisions associated with these two main reasons for tooth loss, increase with age. For that reason, the study of this condition is more relevant in this population and is of great interest, because no previous studies have documented the oral health status of rural older people living in poverty. The aim of this study was to document the oral health status of older people living in poverty in rural areas of Mexico and to evaluate the level to which this important health need is covered through effective interventions, such as dental prostheses.

This study is an analysis of the 2007 *Oportunidades* Evaluation Survey (ENCEL-2007) conducted in low-income households from 741 rural communities (localities with <2,500 inhabitants) in 13 Mexican states. All households of the localities visited were included. The survey consisted of a face-to-face interview divided into household and individual questionnaires. The household questionnaire included general topics, such as physical characteristics of the household and ownership of consumer goods, which were combined thorough factor analysis to construct an asset index. The individual questionnaire addressed the health status of people aged 65 and older. Dependent variables in the analyses were self-report of tooth loss (loss of all natural teeth) and coverage of edentulism treatment (individuals with total loss of their natural teeth who had dental prostheses). For both variables, multivariate logistic regression models were adjusted.

A total of 12,146 elderly people were surveyed; 850 (7%) had cognitive impairment, evaluated using a modified version of the Mini-Mental State Examination,[5] or some visual or hearing impairment (with no caregiver) and were excluded from the analyses. The mean age was 73.52 (median 73), 47.76% were female, and 30.29% were indigenous. Of the rest (11,296), only 6.3% reported that they still had all teeth; 21.8% had lost one to four teeth, 23.5% five to 15 teeth, and 28.9% 16 to 31 teeth, and 19.45% were edentulous. Of the edentulous, 44.3% had dental prostheses.

Sex, age, and smoking were associated with tooth loss indicator, adjusting for the effect of medical insurance and household asset index. Indigenous people and those having paid work had less probability of being edentulous (Table 1). Not surprisingly, the analysis showed that age was positively and significantly associated with edentulism (odds ratio (OR) = 1.06). Tooth loss was more prevalent in women (OR = 1.74).

The analysis of the coverage of edentulism treatment (Table 1) showed some social inequalities, because coverage tends to be lower in more-vulnerable populations: those

Table 1. Factors Associated with Tooth Loss and Coverage of Edentulism Treatment

Factor	Odds Ratio (95% Confidence Interval)
Tooth loss (n = 11,296)*	
Female	1.74 (1.55–1.97)
Age	1.06 (1.05–1.07)
Smoking index†	1.07 (1.02–1.12)
Indigenous	0.69 (0.58–0.83)
Remunerated work	0.68 (0.59–0.79)
Coverage of edentulism treatment (n = 2,171)*	
Female	1.36 (1.12–1.64)
Age	1.62 (1.26–2.09)
Age^2	0.99 (0.99–1.00)
Indigenous	0.49 (0.39–0.61)
Literate	1.74 (1.43–2.11)
Functionally dependent	0.72 (0.58–0.89)
Use of oral healthcare services in previous 12 months	1.61 (1.20–2.18)

*Adjusted for socioeconomic status and health insurance.
†(Number of cigarettes × number of years smoking)/20.
Standardized variable.