Scientific Article

Salivary factors in children and adolescents with insulin-dependent diabetes mellitus

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Abstract

To determine whether hyperglycemia in IDDM (insulin-dependent diabetes mellitus) could interfere with salivary secretion rates, salivary glucose levels, and salivary microbial counts, we studied salivary factors in two groups of children and adolescents with IDDM. One study group included 14 children with newly diagnosed IDDM (mean age 11 years, SD ± 2.4 years). Samples of saliva were collected on admission to hospital and after 2 weeks on insulin treatment. The other study group were 50 IDDM children (mean age 14.4 years, SD ± 1.7 years, mean duration of diabetes 6.2 years, SD ± 1.4 years) visiting the outpatient diabetic clinic. Samples of saliva were collected during two visits, approximately 3 months apart. In the newly diagnosed IDDM cases, mean salivary glucose level decreased from 54.1 ± 31.7 mg/l to 35.2 ± 29.5 mg/l ($P = 0.096$) after beginning insulin treatment. During hyperglycemia, salivary glucose levels correlated with mean blood glucose levels for the day concerned ($r = 0.65$, $P < 0.05$). The results suggest that high blood glucose levels can increase salivary glucose levels. Stimulated saliva secretion increased significantly from 5.4 ± 3.3 ml/5 min to 7.3 ± 2.6 ml/5 min ($P < 0.01$) while glucose balance improved. In the long-term IDDM cases, salivary flow rates and salivary glucose levels were not significantly related to the glycosylated hemoglobin (HbA_1) values. Salivary glucose levels and salivary secretion rates were inversely correlated ($P < 0.05$). In conclusion, hyperglycemia was observed to be associated with decreased salivary secretion and high salivary glucose levels. As a consequence, salivary lactobacilli and yeast counts tended to increase. (Pediatr Dent 18:306–7, 1996)

Most results relating to salivary factors in diabetics stem from studies comparing diabetic and nondiabetic subjects. Lower salivary flow rates in diabetics than in controls[1–6] have not been confirmed by various investigations.[7–12] Many studies[3,5,8,13–17] have found higher salivary glucose levels in diabetics than in controls, but there are exceptions.[8,10] Most studies have found no correlation between blood glucose and salivary glucose.[3,8,13,14] Slight correlations have been reported by Reuterving et al.,[18] Borg and Birkhed,[19] and Darwazeh et al.[17]

Limited studies on the relationship between diabetic status and salivary factors have provided conflicting results. Harrison and Bowen[16] reported lower salivary flow rates in poorly controlled diabetics than in well-controlled diabetics; Reuterving et al.[18] did not. Salivary glucose levels were found to be related to the control of diabetes in some studies[16,18] but not by Darwazeh et al.[17]

Oral candida colonization has been studied more[17,20–25] than salivary lactobacilli counts[4,9,10,26] in diabetics. The few studies relating salivary candida and lactobacilli counts to the level of metabolic control of diabetes provide conflicting results.[21–24]

Divergent results in previous studies may be related to cross-sectional designs, which do not account for intraindividual variations. Because of growth and variations in physical activity in children and adolescents, adjustment of insulin therapy is difficult, and short- and long-term glucose imbalances obviously occur.

To determine whether variation in glucose balance has any effect on salivary factors, we conducted a study similar to those previously undertaken by Reuterving et al.[18] and Twetman et al.[27] Our study had two parts. First, salivary flow rates, salivary glucose levels, and salivary candida and lactobacilli counts were determined in children and adolescents who had received insulin for months or years. Second, to assess the effects of extreme diabetes with severe hyperglycemia and insulin deficiency, the same parameters were monitored in subjects at the time of initial diagnosis of diabetes and after introduction of insulin treatment.

Methods and materials

The first study group, the long-term IDDM (insulin-dependent diabetes mellitus) cases, consisted of 50 diabetic children and adolescents (20 female, 30 male). They were a random sample from all those patients aged 12–18 years old visiting the outpatient diabetic clinic of the hospital for their routine check-ups dur-

ing the study period. Their mean age (± SD) was 14.4 ± 1.7 years (range 11.7–18.4 years). Two examinations were undertaken 3.3 ± 1 months apart. The mean duration of diabetes (± SD) was 6.2 ± 1.4 years. During this period, subjects had received insulin.

The second study group — the newly diagnosed IDDM cases — consisted of 14 subjects (mean age 11.0 ± 2.4 years, range 6.3–14.6 years), seven were boys and seven girls. All new diabetics older than 6 years old during the study period were included. Each was examined twice. The first examination (examination 1) was carried out at the time of the diagnosis of IDDM, on the third day (3.1 ± 1 day) of hospitalization. The second examination (examination 2) was performed on the day of leaving the hospital (12.4 ± 1.6 days later). Accordingly, the mean follow-up period was 9.3 days. Insulin treatment was started on the day of admission to the hospital. The children were otherwise healthy, and not receiving any medications other than insulin.

The procedures, possible discomforts or risks, as well as possible benefits were explained fully to all subjects, and informed consent was obtained prior to investigation.

Paraffin-stimulated whole saliva samples were collected for 5 min at least a half hour after the last meal between the hours 10 am and 2 pm. Amounts of saliva were recorded (ml/5 min) and Dentocult® LB and Oricult® N dip-slides were prepared and incubated at 37C° following the instructions of the manufacturer (Orion Diagnostica, Espoo, Finland). After incubation, the candida count using Oricult® N, and lactobacilli count using Dentocult® LB were expressed as colony-forming units (CFU) per milliliters of saliva, using a scale of 0, 10^3, 10^4, 10^5, and 10^6. The rest of the saliva was centrifuged either immediately or stored in ice for no more than 2 hr before centrifugation, frozen, and kept at -20°C until glucose determination using a D-Glucose UV™ test kit (Mannheim Boehringer, Germany).

The diabetic state of the newly diagnosed IDDM cases was determined from the mean of four capillary blood glucose measurements done approximately every 2 hr on the day of examination. For the long-term IDDM cases, glycosylated hemoglobin values (HbA_1, %) determined on the day of examination were used as reference values. Values of less than 10% were classified as indicating good control of diabetes, values from 10 to 13% were moderate, and values greater than 13% were classified as poor control of diabetes. On examination 2, HbA_1 value of one of the long-term cases was not available.

Statistical analyses

All results are expressed as means ± SD. Student's paired *t*-test for normally distributed variables or the Wilcoxon's signed rank test for variables with skewed distributions was used to determine the significance of differences between paired comparisons. The Kruskall-Wallis test determined the significance of differences between groups; for comparisons between two groups, Mann-Whitney U-test was applied. Pearson's correlation test was used to calculate correlation coefficients between continuous variables.

Results

Salivary flow rates and diabetic status

During examination 1, the mean salivary flow rate of the newly diagnosed IDDM cases was 5.4 ± 3.3 ml/5 min and it was found to have increased to 7.3 ± 2.6 ml/5 min during examination 2. The difference was significant ($P < 0.01$, paired *t*-test), but an increase in flow rate was not observed in all cases (Fig 1).

In the long-term IDDM cases, the differences in salivary flow rates between well, moderately, and poorly controlled subjects were not significant during exam 1 and 2 (during exam 2, $P = 0.05$, Kruskall-Wallis test).

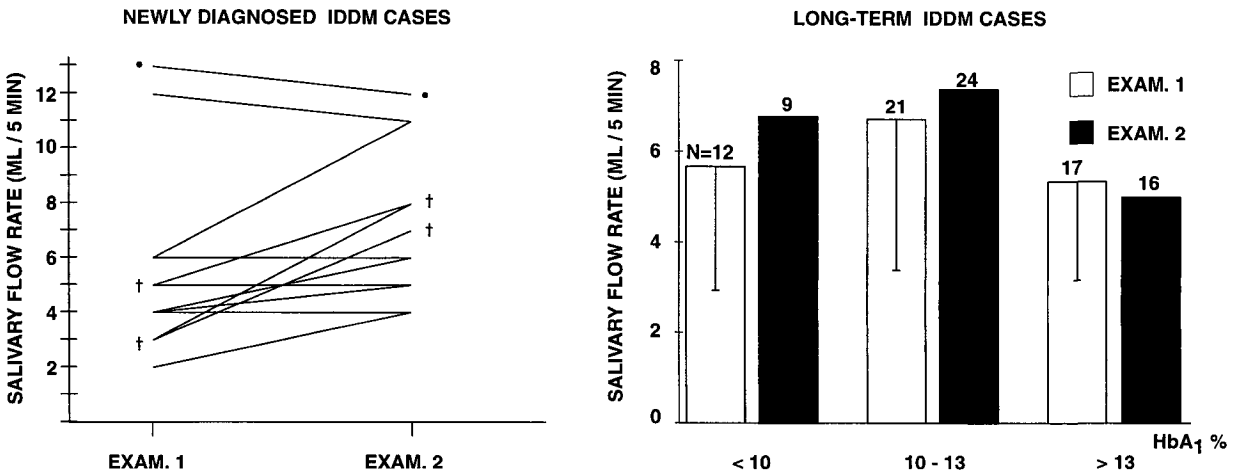

Fig 1. The newly diagnosed IDDM (insulin-dependent diabetes mellitus) cases: salivary flow rates in the hyperglycemic state (exam 1) and after initiation of insulin treatment (exam 2). Each line represents one case, two lines (marked by †) represent two cases each. The long-term IDDM cases: salivary flow rates in well, moderately, and poorly controlled cases, on two examinations (3 months apart).

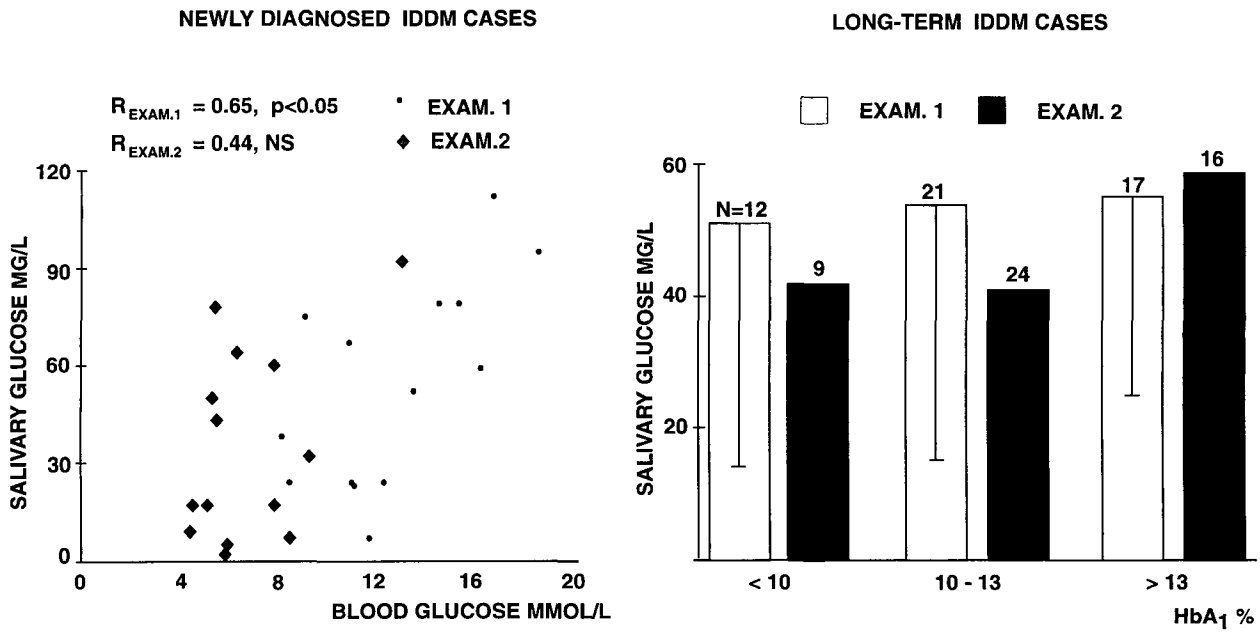

Fig 2. The newly diagnosed IDDM cases: correlation between salivary glucose and blood glucose levels in the hyperglycemic state (exam 1) and after initiation of insulin treatment (exam 2). The long-term IDDM cases: salivary glucose levels in well, moderately, and poorly controlled cases, on two examinations (3 months apart).

Fig 1 shows somewhat lower flow rates in poorly controlled cases compared with moderately or well-controlled cases during both examinations. Salivary flow rates and HbA_1 values did not differ significantly between examinations 1 and 2 (paired *t*-test, $P > 0.05$). Intraindividual variations in flow rates and HbA_1 values were evident in some subjects, but these variations were not correlated.

Salivary glucose and diabetic status

In the newly diagnosed IDDM cases, mean salivary glucose levels decreased from 54.1 ± 31.7 mg/l to 35.2 ± 29.5 mg/l ($P = 0.096$, Wilcoxon's signed rank test). Mean blood glucose on the day of examination 1 correlated with the salivary glucose level ($P < 0.05$); (Fig 2). Between examinations 1 and 2, blood glucose levels decreased significantly, from 12.6 ± 3.2 to 6.7 ± 2.3 mmol/l ($P < 0.001$, paired *t*-test). The decrease in salivary glucose levels correlated with the decrease in mean blood glucose levels ($r = 0.64$, $P < 0.01$).

In the long-term IDDM cases, interindividual variations in salivary glucose levels were considerable, but salivary glucose levels and HbA_1 values were unrelated (Fig 2). Salivary glucose levels, as HbA_1 values, were

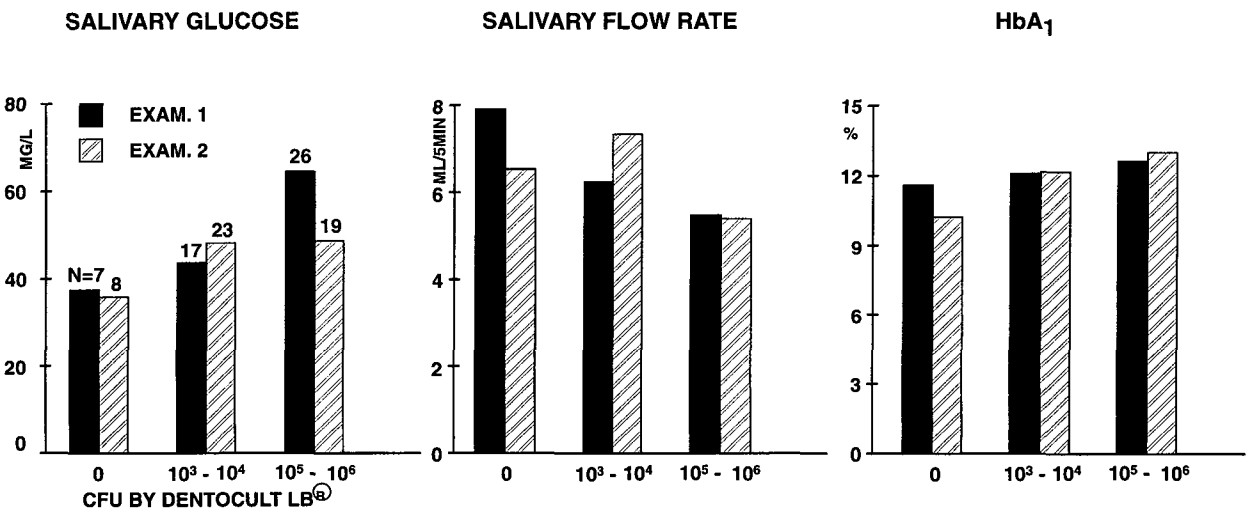

Fig 3. Salivary glucose levels, salivary flow rates, and HbA_1 values in relation to numbers of lactobacilli colony-forming units (CFU) (Dentocult ®LB) in the long-term IDDM cases, on two examinations (3 months apart).

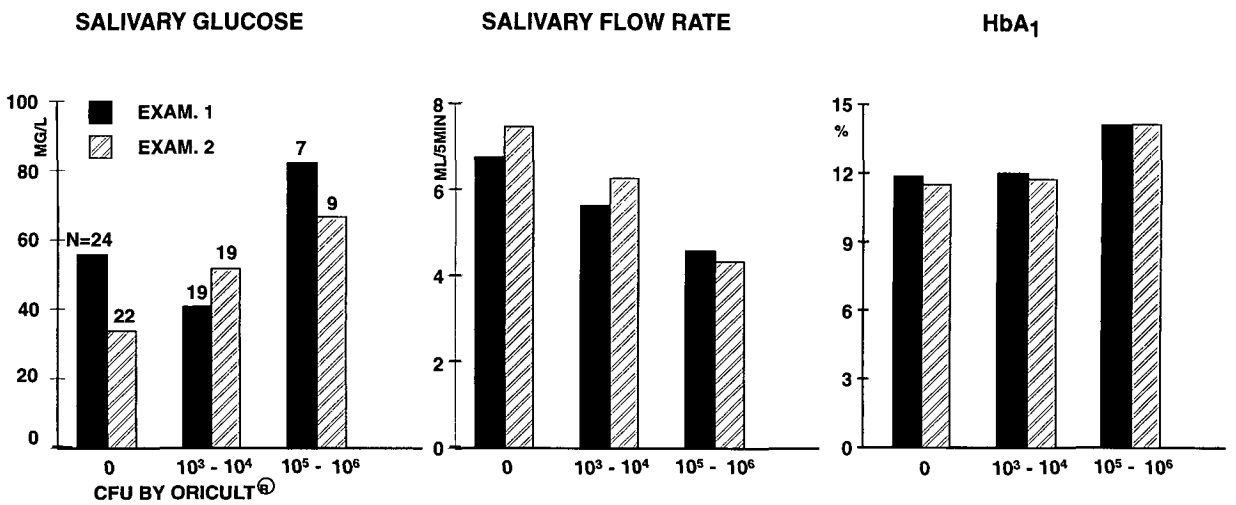

Fig 4. Salivary glucose levels, salivary flow rates, and HbA_1 values in relation to numbers of yeast colony-forming units (Oricult ®N) in the long-term IDDM cases, on two examinations (3 months apart).

not significantly different between the two examinations (Wilcoxon's paired test, $P > 0.05$). Intraindividual variation was observed in some subjects but was not related to changes in HbA_1 values.

Salivary glucose levels versus salivary flow rate

A negative correlation between salivary flow rates and salivary glucose levels was observed during both examinations in the long-term IDDM cases ($r = -0.50$, $P < 0.01$ and $r = -0.33$, $P < 0.05$) and during examination 1 in the newly diagnosed IDDM cases ($r = -0.52$, $P = 0.055$).

Salivary candida and lactobacilli counts and diabetic status

Mean salivary glucose levels, salivary flow rates, and HbA_1 values in various Dentocult® LB and Oricult® N categories in the long-term IDDM cases are shown in Figs 3 and 4. There is a tendency toward higher salivary glucose levels and HbA_1 values, and lower flow rates by increasing microbial counts. The same was clearly observed in the newly diagnosed IDDM cases (data not shown). Lactobacilli counts of seven of the 14 newly diagnosed IDDM cases decreased during follow-up period but remained stable in the others. Oricult® N test was positive in five subjects. All remained positive during follow-up, but in four cases counts were lower during exam 2 than during exam 1.

To test clinical significance, HbA_1 values in subjects with no yeast or lactobacilli growth were compared with those in the subjects with the highest scores. Mean HbA_1 values between the groups in relation to yeast counts differed significantly during both examinations ($11.9\% \pm 2.7\%$ vs. $14.1\% \pm 2.3\%$ during exam 1; $11.5\% \pm 2.1\%$ vs. $14.1\% \pm 2.5\%$ during exam 2, $P < 0.05$, Mann-Whitney U-test). The difference between groups in relation to lactobacilli count was significant only during exam 2 ($10.2\% \pm 2.1\%$ vs. $12.9\% \pm 2.6\%$, $P < 0.05$, Mann-Whitney U-test).

Discussion

This is the first replication study to include a group of subjects at the time of their diabetes diagnosis, and immediately after initiation of insulin treatment. Untreated diabetes represents an extreme disturbance in glucose metabolism with severe hyperglycemia and insulin deficiency. In such subjects, balancing the diabetic state with insulin treatment was observed to increase salivary flow rates and to decrease salivary glucose levels. Previous replicative study[18,27] results were similar, but changes were not as obvious as in our study. An explanation is that Twetman et al.[27] did the first follow-up examination 3 months after initiation of insulin treatment, and most of the subjects in the Reuterving et al.[18] study had been treated with insulin for months or years. Animal studies also support our findings. Insulin deficiency caused degenerative changes in the salivary glands of animals.[28–31] These could cause decreases in salivary flow rates.[32] Such changes are irreversible, but the consequences can be treated with insulin.[28,32,33] Apart from the effect of insulin deficiency on salivary glands, it might be that the overall dehydration associated with hyperglycemia decreased the volume of saliva excreted.

In the long-term IDDM cases, we found no obvious connections between the diabetic state as indicated by HbA_1 values and salivary flow rates or glucose levels. A slight negative correlation between flow rates and HbA_1 values was observed during exam 2. Harrison and Bowen[16] have reported lower salivary flow rates and increased salivary glucose levels in poorly controlled compared to well-controlled young diabetics. The intraindividual variations in salivary flow rates and salivary glucose levels observed in some subjects during follow-up was not related to changes in HbA_1 values. In the long-term IDDM cases, we assessed the diabetic state using HbA_1 values, which reflect the mean blood glucose levels over a considerably long

time period of 1 to 3 months. Differences in results relating to salivary flow rates and HbA_1 values, and the large intra- and interindividual variations in salivary glucose levels observed in our study and others,[9, 18, 19, 27] may indicate that transient short-lasting hyperglycemic phases — not reflected in HbA_1 values — alter salivary flow rates and glucose levels.

Some investigators have reported lower salivary flow rates[1–6] and higher salivary glucose levels[3, 5, 8, 13–17] in diabetics than in nondiabetic controls, while other studies haven't.[7–12] We found that the effect of diabetes on salivary flow rates and glucose levels is not marked and may only be evident during severe hyperglycemia. Variations in levels of metabolic control of the previous study populations could have caused substantial differences in results. Cross-sectional studies — as all previous studies except two[18, 27] have been — may not be accurate, especially in children and adolescents in whom the diabetic state can change rapidly. Age should also not be ignored. This study included only children and adolescents to eliminate possible age-related changes. For example, medications taken in adult populations could decrease salivary flow rates and affect results. Adult diabetics are particularly prone to high blood pressure and have antihypertensive medication, which has not been taken into account in all previous studies.[5–7] No subject in our study was receiving medication other than insulin.

In the newly diagnosed IDDM cases, we observed a decrease in mean salivary glucose after 2 weeks on insulin treatment, while blood glucose levels decreased significantly. Salivary glucose levels and mean blood glucose levels in the hyperglycemic state in the newly diagnosed IDDM cases correlated. Magnitudes of the decreases in salivary glucose and blood glucose levels also correlated with each other. These results suggest that blood glucose levels are related — to a certain extent — to salivary glucose levels. We used means of several blood glucose measurements on the day of examinations. All were constantly high at the beginning of hospitalization and low at the end of the follow-up period. Blood glucose levels can change dramatically in short periods of time depending on the type of insulin used and when it is given, when the last meal was eaten and what was eaten, and on the level and duration of physical activity. Transport of glucose from blood to saliva — most obviously by diffusion — may not be able to reflect minute changes in blood glucose levels. In fact, in healthy subjects after oral intakes of glucose, Borg and Birkhed[19] observed that times when blood glucose levels reflected on salivary glucose levels, exhibited large inter- and intraindividual variation. Therefore, blood glucose levels measured when saliva samples were collected may not be representative, which may be why no correlation between blood and salivary glucose levels has been found in previous studies.[3, 8, 13, 14]

In the newly diagnosed IDDM cases, the magnitude of the decrease in salivary glucose was less than would have been expected on the basis of the change in blood glucose levels. This may indicate that other variables or sources of glucose other than blood are also important. One factor that might have an effect was shown to be salivary flow rate. This correlated negatively with salivary glucose levels in both the long-term and in the newly diagnosed IDDM cases. Variations in salivary flow rates could partly explain the large intra- and interindividual variations observed in salivary glucose, and should be taken into account when studying relationships between blood glucose and salivary glucose levels. Dilution of salivary glucose concentrations by increasing salivary flow rates has been discussed by some investigators,[16, 18, 19, 34] suggesting that glucose diffuses from blood to saliva. Our results do not allow definition of a threshold mechanism connecting blood and salivary glucose levels, but such a mechanism is suggested by some studies.[32, 35]

A trend toward higher salivary glucose levels, lower salivary flow rates, higher mean blood glucose levels in the newly diagnosed IDDM cases, and higher HbA_1 values in the long-term IDDM cases was observed with increasing yeast and lactobacilli counts. The slight relationship observed between microbial counts and HbA_1 values indicates that over long periods of time, subjects with poor control of diabetes have periods of hyperglycemia favoring microbial growth. It is not clear whether hyperglycemia exerts an effect via salivary secretion rates or salivary glucose levels or both. Findings relating to high glucose levels as a promoting factor of yeast adherence and colonization[36, 37] support our result. In previous studies, no correlation between yeast growth and glycemic control (as assessed by HbA_1 values) was found.[23–25] In only one study[25] was density of yeast growth measured as it was in our study. Darwazeh et al.[17] reported higher salivary glucose levels in subjects with yeast growth than with no yeast growth. However, they did not explore whether this was a result of lower salivary flow rate in these subjects. Twetman et al.[4] reported that lactobacilli counts were related to the level of metabolic balance in their cross-sectional study. Swanljung et al.[10] found no correlation between lactobacilli counts and HbA_1 values, but all subjects in their study had well-controlled diabetes. Conflicting results in previous studies may be related to differences in metabolic balance of study populations.

Conclusions

1. Salivary tests performed at the initial diagnosis of IDDM revealed that hyperglycemia was associated with decreased salivary flow rates and increased salivary glucose levels. High blood glucose levels were reflected as high salivary glucose levels.

2. In the long-term IDDM cases, diabetic state — determined by HbA_1 values — was not so clearly related with salivary factors, possibly because HbA_1 values do not indicate short-term hyperglycemic phases.
3. High salivary lactobacilli and yeast counts were associated with decreased salivary flow rates, increased salivary glucose levels, and high HbA_1 values.

This study was supported by The Foundation for Diabetes Research, Tampere, Finland, The Alma and K.A. Snellman Foundation, Oulu, Finland, and the Paulo Foundation, Helsinki, Finland.

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