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Investigations into the relationship between saliva and dental caries.[1]

By

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Salivary influence on the caries process is most clearly demonstrated by the increased caries frequency in cases of either absent or substantially reduced saliva secretion, whether due to pathological conditions in man (PRINZ 1932, BORGMAN 1948) or to experimental removal of the glands in animals (summary: STELLING & GUSTAFSSON 1952). Which salivary factors play the main part in these cases and under normal conditions? Our theories on this question naturally depend on our general concept of the caries mechanism. An overwhelming array of evidence has now accumulated in favour of Miller's chemico-parasitical theory, even if it does not fully explain the initial phase of caries. According to this theory, as well as our present knowledge of salivary physiology and chemistry, the following factors may be held to be of the foremost importance in the formation of acid and dissolution of enamel. Hydrolysis by *amylase* is the first stage in the ntraoral decomposition of starch into simpler sugars and acids. Acidification through these cleavage products may be substantially hampered by a high *pH value* and a strong *buffer effect.* The *calcium* and *phosphate* content should in theory counteract dissolution of the calcium phosphate, the chief constituent of the dental hard tissues. The *rate of secretion* should be of significance for diluting and rinsing away the substrate and products of the acid-forming bacteria. *Mucin* makes the saliva viscous, thereby

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retarding flow and diffusion; new investigations indicate, moreover, that mucin can serve both as a substrate for bacteria (ROGERS 1948) and as an inhibitor of salivary lysozyme (SIMMONS 1952).

The numerous experiments which have sought to correlate the incidence of caries with the above-named saliva factors may be appraised briefly as follows (the references cited cover more or less complete surveys). Amylase: varying and conflicting reports (ERICSSON 1951). pH value and buffer effect: negative correlation with incidence of caries, but seldom of statistical significance (ERICSSON 1949). Calcium, phosphate: also negative correlation, but even less significance (ERICSSON 1949). Mucin, viscosity: positive correlation, attained however by methods involving large sources of error (ERICSSON & STJERNSTRÖM 1951, RATHJE 1951).

The chief aim of this investigation has been to study the correlation of salivary glucose and lactate clearances with other saliva factors and with the caries incidence. The term oral glucose clearance was coined by VOLKER and PINKERTON (1947: 22, 23), who investigated the percentage of reducing sugar in saliva after ingestion of different carbohydrates. Earlier, TEUSCHER and FOSDICK had made investigations along the same line (1937: 20, 21). ERICSSON, working on salivary amylase, used a similar technique (1951), and LUNDQVIST pursued the same idea on a larger scale while engaged in the Vipeholm investigations (1952).

The effect of ingesting different carbohydrates on the lactic acid content of the saliva was first studied by NEUWIRTH and KLOSTERMAN (1940) and later more exhaustively by ERICSSON and HELLSTRÖM (1950, 1952).

A study of the course of both substrate clearance and lactic acid clearance in individual cases and larger groups, promised reward, since strong evidence had been presented in support of the theory that the dissolution of enamel by caries is a relatively acute and intermittent process, limited to short intervals after ingestion of carbohydrate when the changes in the sugar and lactic acid content of the saliva are most pronounced (STEPHAN 1940, ERICSSON 1949, LUNDQVIST 1952).

Theoretically, it seemed quite probable that a correlation could exist between glucose clearance and formation of lactic acid, and between each of these factors and some other saliva factors. The amylase activity might be assumed to affect first of all the salivary sugar content after ingestion of starch; further, the rate of secre-

tion and flow could well affect both glucose and lactate clearances. The secretion rate, viscosity and amylase activity seemed, therefore, to be the salivary factors worth closest study in connection with glucose clearance and formation of lactic acid. Finally, it seemed advisable at the same time to study the possible correlation of all these saliva factors with incidence of caries.

Material.

The experiments were carried out on persons between the ages of 20 and 30 with extreme caries conditions. Most of the subjects chosen were students enrolled at the College of Dentistry and other colleges in Stockholm, and student nurses at the College of Dentistry. Subjects with less than 15 predilection surfaces that were either carious, filled or lost by extraction (DMF surfaces, not counting wisdom teeth) were designated as *caries-resistant.* During the last few years, each subject in this group had had an average of less than two new cavities per year. Persons belonging to the experimental *high-caries* group had more than 55 DMF surfaces; during the last few years, they had acquired an average of more than five new cavities per year.

The material comprises 31 subjects in the caries-resistant group and 32 in the high-caries group; the former numbered 8 women and 23 men, the latter 17 women and 15 men.

The mean of the caries index (according to the 100-surface system) is 0.08 (0.00—0.16) for the caries-resistant and 0.70 (0.58—0.86) for the high-caries group.

Certain minimum health requirements were demanded of the subjects in order to exclude factors which might have influenced the caries picture through impaired general health, gingival disorders on an endogenous basis, or pathologically influenced saliva. Thus, none of the participants were to have had diseases requiring long confinement in bed; no stomach or intestinal diseases, no diabetes, nephritis, anaemia or any other kind of blood disease; no medication with hydrochloric acid, iron salts, atropine, belladonna or other medicines having pronounced effects on the autonomic nervous system; and no cases of pregnancy.

A further requirement was that none of the subjects was to have indulged in extreme habits during the last five years with respect to frequency of carbohydrate ingestion, fruit consumption

and use of tobacco. Excessive brushing of the teeth was a disqualifying factor for the caries-resistant group, and the opposite for the high-caries group. Extreme exogenous influences were thus excluded as far as possible.

Methods.

Clinical examinations of all subjects were performed by one of the authors (L. S.), and covered status with respect to caries, gingiva and occlusion.

All subjects were required to give anamnestic accounts covering: places of birth and rearing, later places of residence and their dates, and condition of health from birth to the date of examination. Special importance was attached to any factors which could reasonably be expected to affect the secretion of saliva. Dietary anamnesis included times of main meals, times and composition of in-between meals, and other consumption of substances containing sugar and starch. In respect to oral hygiene note was made of the present and previous frequency of tooth-brushing, the subjects' own valuation of the effectiveness of their mouth hygiene, as well as the amount of dental care they had obtained. The dental treatment was specified in greater detail for the last few years, this making it possible to follow the recent development of caries in the subjects.

Saliva samples for the analyses were taken without stimulation and at a fixed time, 10 a. m. Subjects were not permitted to eat, smoke or brush their teeth for one hour prior to sample-taking. While in a relaxed state with their lips closed, the subjects let saliva accumulate in their mouths and then let it drip passively in a measuring glass. The time needed to collect 1.5 ml of saliva was noted in order to determine *rate of secretion;* this volume was then transferred to a Hess viscosimeter (ERICSSON & STJERNSTRÖM 1951). Actually, it is not the viscosity as such that is measused here, but its reciprocal, the *flow*. This was measured at room temperature every 10th minute for one hour, counting from the beginning of the secretion period. This method was adopted because wide variations in the secretion time were expected from the subjects: in view of the spontaneous reduction in viscosity, the comparison between individuals and groups had to take place at a standardized time after the start of secretion (ERICSSON & STJERNSTRÖM 1951). The figures given in the results correspond

to 25 cm of water, making the relative viscosity 25: (salivary flow reading).

When another 2.5 ml of saliva had accumulated in the measuring glass, 1 ml was pipetted and diluted with 2 ml distilled water for the estimation of *amylase*. This was done by analyzing the quantity of reducing sugar liberated by 1 ml of this diluted saliva from 100 ml of 1 % starch solution during a two-minute incubation period at a temperature of 37°. The starch solution was buffered at pH 6.8 by 0.005 M phosphate buffer, and contained 0.5 % NaCl.

1 ml of the saliva was used for determining the *fasting value of the reducing substance*, calculated as mg glucose/100 ml, in accordance with the colorimetric method of FOLIN and WU (1920). This volume was immediately pipetted into 2 ml HCl solution (0.30 ml 0.1-n HCl + 1.70 ml dist. water) in order to stop enzyme activity and to precipitate the protein of the saliva at its isoelectric point (ARNOLD & MCCLURE 1941).

0.2 ml of the saliva obtained was used to determine the *fasting value of lactate* in accordance with BARKER and SUMMERSON's colorimetric method (1941). Here the saliva was immediately pipetted into 0.5 ml of 20 % $CuSO_4 \cdot 5\,H_2O$ in order to check further enzyme activity.

After some minutes of rest, the subjects were permitted to eat white bread for two minutes. A few seconds before these two minutes were up, the subjects were made to swallow and then to remove bread crumbs from their teeth with a few simple movements of tongue and lips. The times for the following sample removals have been counted from the end of this operation.

The subjects were not allowed to rinse their mouths during the experiment.

During the next half-hour, samples of rest saliva were taken at intervals of 2, 5, 10, 20 and 30 minutes after completed ingestion of bread. The two-minute sample included the quantity of saliva accumulated between $1^1/_2$ and $2^1/_2$ minutes, the five-minute sample between $4^1/_2$—$5^1/_2$ minutes, etc.

0.2 ml of each sample was immediately pipetted into HCl solution for analysis of *reducing sugar* in accordance with FOLIN and WU. Dilutions:

2 and 5 min. samples { 0.2 ml saliva; 0.5 » 0.1-n HCl; 9.3 » dist. water } = dil. 1 : 50

Table 1.

Comparison of caries groups.

		Secr. rate			Flow						Amylase
		Both sexes	Male	Fem.	10 min.	20 min.	30 min.	40 min.	50 min.	60 min.	
Low caries group	n	32	24	8	18	30	32	32	32	32	32
	Max.	10.0	10.0	4.0	20.5	20.5	20.6	20.6	20.5	20.6	183.6
	Min.	1.0	1.0	1.5	1.1	1.8	2.1	2.3	2.7	2.9	3.9
	Med.	4.08	4.68	2.28	9.07	9.91	11.05	11.80	12.78	13.22	75.33
High caries group	n	31	14	17	12	27	29	30	30	30	31
	Max.	7.5	7.5	6.0	16.8	16.9	17.5	18.3	18.0	18.0	297.3
	Min.	0.4	1.5	0.4	0.8	1.0	1.2	1.2	1.3	0.1	18.0
	Med.	3.32	3.99	2.77	9.76	8.62	9.31	9.65	10.07	10.03	76.04
Comparison between groups	t	1.37	0.864	0.795			1.69				
	P	0.1—0.2	0.3—0.4	0.4—0.5			0.05—0.1				
	Sign.										

Table 1 (contd.).

Glucose							Lactate						
Fasting	2 min.	5 min.	10 min.	20 min.	30 min.	% red. 2—5 min.	Fasting	2 min.	5 min.	10 min.	20 min.	30 min.	% red. 5—20 min.
32	31	31	32	31	30	30	31	32	32	32	32	32	32
6.5	605.0	305.0	160.8	64.5	21.0	100.0	0.48	4.35	5.97	4.86	3.35	2.51	99.3
1.2	5.0	0	0	0	0	— 3.3	0	0.15	0.29	0.21	0.01	0	— 136.5
3.44	206.11	98.37	51.37	12.41	5.57	49.73	0.07	1.38	1.95	1.74	0.89	0.49	49.16
31	29	30	29	27	28	28	31	31	31	31	30	29	30
10.4	1,175.0	720.0	348.9	148.5	73.5	74.7	1.22	5.61	6.54	8.70	10.08	7.17	88.2
1.1	49.0	11.0	1.5	0.8	0	— 28.6	0	0.42	0.46	0.41	0.22	0.10	— 125.5
3.85	288.33	181.60	91.00	32.12	11.83	36.88	0.17	1.79	2.55	2.42	2.02	1.50	25.99
	1.60	2.51	2.02	2.39	2.07	1.90		1.44	1.62	1.67	2.81	2.67	2.01
	0.1—0.2	0.01—0.02 *	0.02—0.05 *	0.02—0.05 •	0.02—0.05 •	0.05—0.1		0.1—0.2	0.1—0.2	0.1	0.001—0.01 **	0.001—0.01 **	0.02—0.05 *

10, 20 and 30 minute samples	0.2 ml saliva 0.15 » 0.1—n HCl 2.65 » dist. water	= dil. 1 : 15

0.2 ml of each saliva sample was immediately pipetted into a copper sulphate solution for *lactate* analysis in accordance with the above.

Results.

The results of the saliva analyses are summarized in Table 1 together with a statistical evaluation, using Student's t-test, of the differences between the two groups. The 30-minute flow values were chosen for comparison, because sufficient volumes for determination were obtained at this time in all but two cases; extrapolated values for these two cases were, however, also included in this comparison. Calculation of viscosity in terms of reciprocal flow values seemed unprofitable, since the fluidity of the saliva as obtained from the Hess viscosimeter could just as well be combined directly with the other factors. For reducing sugar and lactate, the percentage reduction was calculated for the intervals of most pronounced decrease.

Since the sex distribution differed between the two caries groups, the analytical values of males and females were compared within each group. There appeared a difference in secretion rate which was almost significant in the low-caries group (Tab. 2). On account of this difference — to be commented on in the discussion — the secretion rates of sexes are also compared separately

Table 2.

Sex differences in secretion rate.

	Low caries group		High caries group	
	Male	Female	Male	Female
n	24	8	14	17
Max.	10.0	4.0	7.5	6.0
Min.	1.0	1.5	1.5	0.4
Med.	4.68	2.28	3.99	2.77
t	2.614		1.857	
P	0.01—0.02		0.05—0.1	
Signif.	*			

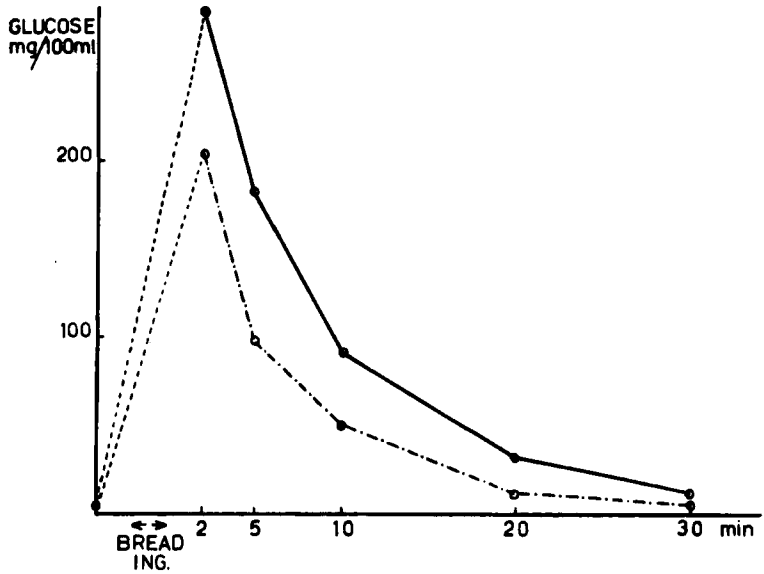

Fig. 1. Average salivary glucose values for susceptible group (————) and resistant group (—·—).

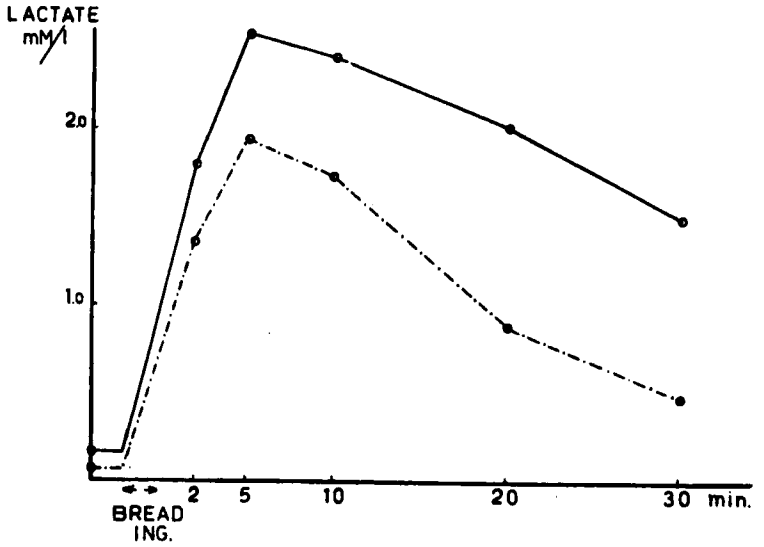

Fig. 2. Average salivary lactate values for susceptible group (————) and resistant group (—·—).

in Table 1. No significant sex difference or definite trend was found for the other analytical values.

It appears from Table 1 that the low caries group has throughout the theoretically more favourable values: higher secretion rate, lower viscosity, lower glucose and lactate values and more rapid reduction of these values. There is no difference between the group averages for the amylase activity.

The most significant differences are found for salivary sugar and lactate content. (** denotes "significant difference", $0.001 < P < 0.01$; * denotes "almost significant difference", $0.01 < P < 0.05$). Figs. 1 and 2 illustrate the averages of the two groups.

A graphic representation of flow, glucose and lactate values, which was made as a preliminary to the statistical treatment, revealed that of 13 cases with specially viscid saliva 11 belonged to the high-caries group.

Table 3 gives the correlations between some of the saliva factors. The analytical values to be compared were chosen on the following grounds. Secretion rate was combined with flow and amylase activity (columns a, d), since it has been previously reported that both these factors increase with stimulation of secretion in the individual (ERICSSON 1951, RATHJE 1951, ERICSSON & STJERNSTRÖM 1951). The 2-minute glucose values were combined with the amylase figures (g), since the amylase activity might be expected to influence the reducing sugar level, especially during the first minutes after the ingestion. The 20-minute and 30-minute lactate values were chosen because the greatest differences between groups and individuals occurred at these intervals; they were combined with the 10-minute glucose values (h, i) on account of the lag of the lactate maxima in relation to the sugar values. The reasons for the choice of the other values for comparison (b, c, e, f) have been given in the introduction. The significance of the correlation coefficients has been calculated according to Student's t-test. Asterisks in Table 3 have the same meaning as in Table 1.

Significant positive correlations are found for sugar and lactate concentrations. The correlations between secretion rate and glucose and lactate reductions are all positive but in no case significant. There are tendencies towards positive correlations between secretion rate and flow, and between flow and glucose and lactate reductions.

Table 3.

Correlations between salivary factors.

		a Secr. rate — Flow 30 min.	b Secr. rate — Glucose red. 2—5 min.	c Secr. rate — Lactate red. 5—20 min.	d Secr. rate — Amylase	e Flow 30 min. — Glucose red. 2—5 min.	f Flow 30 min. — Lactate red. 5—20 min.	g Glucose 2 min. — Amylase	h Glucose 10 min. — Lactate 20 min.	i Glucose 10 min. — Lactate 30 min.
Low caries group	n	32	30	32	32	30	32	31	32	32
	r	0.015	0.28	0.139	0.172	0.154	— 0.030	— 0.167	0.828	0.90
	P	> 0.1	> 0.1	> 0.1	> 0.1	> 0.1	> 0.1	> 0.1	< 0.01	< 0.01
	Sign.								**	**
High caries group	n	29	28	30	31	28	29	29	28	27
	r	0.343	0.038	0.334	— 0.367	0.232	0.200	0.165	0.468	0.755
	P	0.05—0.1	> 0.1	0.05—0.1	0.02—0.05	> 0.1	> 0.1	> 0.1	0.01—0.02	< 0.01
	Sign.				*				*	**

Table 4.

Case history factors.

	Health	Occlusion, articulation	Diet	Oral hygiene
Low caries group	14 —	35 —	17 —	17 —, 5 +
High caries group ...	10 —	39 —	24 —	6 —, 12 +

The case histories were specially revised for the following factors which could be supposed to have contributed to the caries situation of the subjects: general health, occlusion and articulation, diet and mouth hygiene. The findings were estimated and tabulated in the following way:

health: 1—3 minus signs for factors which had impaired the general state of health for any appreciable time or led to hospitalization;

occlusion — articulation: 1—3 minus signs for disturbances which might have impaired the function and self-cleaning of the teeth;

diet: 1—3 minus signs for carbohydrate ingestions between meals;

mouth hygiene: 1—2 minus or plus signs for a standard below or above one daily tooth-brushing, respectively.

The sums of minus and plus signs for the two groups are given in Table 4. Of the results, which must of course be judged with great caution on account of their partly subjective background, the most striking is the difference in mouth hygiene in favour of the high-caries group. This group also has the more favourable record regarding general health, while articulation and dietary data are better for the low-caries group.

Discussion.

The results of this investigation should naturally be seen in the light of the previous knowledge of intraoral enzymatic acid formation and salivary influences on this process. The following may be said to be the most immediate theoretical expectation regarding the rôle of the factors analyzed in this investigation. A high amylase activity makes for a rapid saccharification of ingested starch and a high immediate salivary level of reducing sugar, but also for a rapid elimination of the starch from the oral cavity. A high level of reducing sugar in the saliva means a rapid dif-

fusion into the dental plaque and other oral bacterial deposits, resulting in rapid acid formation. This is reflected in a high lactate content in the saliva through diffusion from the deposits (ERICSSON & HELLSTRÖM 1952). On the other hand, a high salivary secretion rate makes for a rapid washing away of both sugar and lactate, as does a low viscosity of the saliva.

Assuming this course to be of crucial importance in the development of caries, all the differences found between the two groups in this investigation tend in the theoretically expected direction. The most important result is the strong connection between the salivary glucose and lactate levels, and between both factors and the caries picture. This confirms the impression that the intraoral sugar time (LUNDQVIST 1952) and acid production are the most important causal factors in dental caries. It also indicates that individual differences in the carbohydrate clearance may play an important part in the susceptibility to dental caries. It would, of course, be of great interest to study as well the effects of sucrose ingestion on salivary glucose and lactate clearances.

The small differences in secretion rate and flow between the caries extremes agree with the findings in numerous investigations on salivary pH, buffering, calcium and inorganic phosphate (ERICSSON 1949): the differences regularly go in the expected direction, but the statistical significance is in most cases rather weak. A possible explanation of this fact lies in the complexity of the caries process, where bacterial, dietary, gingival and enamel factors, to mention just the most obvious, also play their part. It is clearly difficult to prove the effect of one single factor in such a context.

The difference in secretion rate between the sexes was found to be rather great in this material. BECKS and WAINWRIGHT (1943), in a much larger material, found rather small and statistically non-significant differences between the sexes in all ages. The difference may simply depend on the smaller size of the female subjects — or their heads and salivary glands — and may have been especially large due to random factors in this particular investigation.

The revelation, in the survey of the case histories, of better average mouth hygiene in the high-caries group indicates that this factor is not particularly significant in the development of caries or lactic acid formation.

Summary.

The secretion rate, flow and amylase activity of the saliva, and its glucose clearance and lactate content after bread ingestion, were analyzed in 63 subjects between 20 and 30 years of age, about equally divided between one group with very high and one with very low caries frequency. The susceptible group was found to have higher average sugar and lactate levels in the saliva during the half-hour immediately following the ingestion. Positive correlations were found in both groups between glucose and lactate contents. These differences and relationships were statistically significant.

Non-significant trends were found towards higher values for secretion rate and flow for the resistant group, and also towards positive correlations between secretion rate and flow on the one hand, and glucose and lactate elimination on the other. The amylase activity showed no differences between the groups, and no consistent relationship to the other factors.

Zusammenfassung.

Sekretionsgeschwindigkeit, Fliessvermögen und Amylasewirkung des Speichels, gleichwie Glucoseclearance und Lactatgehalt nach Brotzufuhr, wurden analysiert bei 63 Versuchspersonen zwischen 20 and 30 Jahren, verteilt auf zwei etwa gleich grosse Gruppen mit sehr hoher bzw. sehr niedriger Kariesfrequenz. Es wurde gefunden, dass die kariesempfängliche Gruppe eine halbe Stunde unmittelbar nach dem Zufuhr durchschnittlich höhere Zucker- und Lactatwerte im Speichel hatte. Positive Korrelation zwischen Glucose- und Lactatgehalt wurde in beiden Gruppen gefunden. Diese Unterschiede und Korrelationen waren statistisch signifikant.

Nicht-signifikante Tendenz zu höheren Werten für Sekretionsgeschwindigkeit und Fliessvermögen wurde in der resistenten Versuchsgruppe gefunden, wie auch Tendenz zu positiven Korrelationen zwischen Sekretionsgeschwindigkeit und Fliessvermögen auf der einen Seite, Glucose- und Lactatelimination auf der anderen. Die Amylasewirkung zeigte keinen Unterschied zwischen den Gruppen und keinen konstanten Zusammenhang mit den übrigen Faktoren.

Résumé.

La vitesse de sécrétion et de coulage, l'action d'amylase et la clearance de glucose et d'acide lactique après ingestion de pain ont été étudiées chez 63 sujets ayant entre 20 et 30 ans, répartis à peu près également en un groupe à fréquence de carie très haute et un groupe à fréquence très basse. On a constaté que le groupe susceptible avait en moyenne des titres de glucose et de lactate plus hauts pendant la demi-heure suivant immédiatement l'ingestion que ne l'avait le groupe résistant. Des corrélations positives ont été trouvées dans les deux groupes entre les titres de glucose et de lactate. Ces différences et corrélations étaient statistiquement significatives.

Des tendances non-significatives ont été trouvées pour de plus hautes valeurs de vitesse de sécrétion et de coulage dans le groupe résistant, et aussi pour des corrélations positives entre la vitesse de sécrétion et de coulage d'un coté, l'élimination de glucose et de lactate de l'autre. L'action d'amylase n'a montré aucune différence entre les groupes ni aucun rapport constant avec les autres facteurs examinés.

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