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ORIGINAL COMMUNICATION

High intakes of milk, but not meat, increase s-insulin and insulin resistance in 8-year-old boys

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Objective: Our objective was to examine if a high animal protein intake from milk or meat increased s-insulin and insulin resistance in healthy, prepubertal children. A high animal protein intake results in higher serum branched chain amino acids (BCAA; leucine, isoleucine and valine) concentrations, which are suggested to stimulate insulin secretion. Furthermore, milk possesses some postprandial insulinotrophic effect that is not related to its carbohydrate content.
Design: A total of 24 8-y-old boys were asked to take 53 g protein as milk or meat daily. At baseline and after 7 days, diet was registered, and insulin, glucose, and amino acids were determined. Insulin resistance and beta cell function were calculated with the homeostasis model assessment.
Results: Protein intake increased by 61 and 54% in the milk- and meat-group, respectively. In the milk-group, fasting s-insulin concentrations doubled, which caused the insulin resistance to increase similarly. In the meat-group, there was no increase in insulin and insulin resistance. As the BCAAs increased similarly in both groups, stimulation of insulin secretion through BCAAs is not supported.
Conclusions: Our results indicate that a short-term high milk, but not meat, intake increased insulin secretion and resistance. The long-term consequences of this are unknown. The effect of high protein intakes from different sources on glucose–insulin metabolism needs further studying.
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Introduction

When expressed per kg body weight, the protein intake in children is considerably higher than in adults, and infants and children receive typically 2–3 times as much as their physiological requirement (Rolland-Cachera *et al*, 1999). However, there is a wide variation in protein intake, and some infants have an intake as high as of 5–6 g/kg (Rolland-Cachera *et al*, 1999). It is unknown to what degree protein intake and protein quality have a regulatory effect on growth factors, such as insulin, in well-nourished children with a protein intake far above their physiological requirements.

A high intake of animal protein is likely to result in higher concentrations of serum branched chain amino acids (BCAA; leucine, isoleucine and valine). BCAAs are suggested to stimulate secretion of insulin (Chaussain *et al*, 1980; Axelsson *et al*, 1989) and thereby increase serum concentrations of insulin and possibly insulin resistance. Insulin resistance is a well-known factor in the development of non-insulin dependent diabetes mellitus (NIDDM) (DeFronzo, 1992).

However, the effect of animal protein quality on insulin response is not completely elucidated. In a study based on regular or fermented milk products (Ostman *et al*, 2001), a discrepancy between glycemic index (GI) and insulinemic index (II) was found; despite very low GIs (GI = 15–30), high

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IIs were found (II = 90–98) for both milk and yoghurt. From this study, it was concluded that the insulinotrophic effect was not related only to the carbohydrate component of milk, but also to some yet unidentified food component. Also, in another study of postprandial glucose and insulin responses, addition of even an ordinary amount (200 ml) of milk increased the insulin response (+300%) to a low-GI meal to the same level as seen with very high-GI white bread meal (Liljeberg & Bjorck, 2001). Thus, the mechanism for the insulinotrophic effect of milk is not known. Whether the effect of milk is not only observed postprandially, but also on fasting values of insulin, and whether the effect of milk differs from the effect of meat as well as the potential long-term metabolic consequences need to be elucidated.

Objective

We have performed an intervention study, in which 8-y-old boys were given animal protein as either milk or meat for 1 week. The aim of the study was to examine whether an increase in animal protein intake—as either milk or meat—could increase fasting concentrations of the growth factors, insulin and insulin-like growth factor I (IGF-I) in healthy, prepubertal boys. We have previously shown that concentrations of IGF-I and IGF binding protein-3 (IGFBP-3) increased significantly after 1 week with milk, but not with the same amount of animal protein as meat (Hoppe *et al*, 2004). In the present paper, we present data on fasting concentrations of insulin, and insulin resistance and beta cell function, as assessed by calculation with the homeostasis model assessment (HOMA) from fasting concentrations of glucose and insulin.

Subjects and methods

As previously described (Hoppe *et al*, 2004), 24 8-y-old boys were asked to take about 53 g protein daily, 12 boys as 1. 5 l of skimmed milk, and 12 other boys as 250 g low fat meat. The milk and the meat supplements were provided to the children from the Department. In addition, they were asked to eat their normal diet *ad libitum*.

The subjects were recruited in the following manner: boys born between October and December 1992 were drawn at random from the Central Personal Register, and were invited to participate in the study. Children with a habitual milk intake of 500 ml/day or less, who were willing to increase their intake of milk or meat considerably during a week, were eligible for the study. Children with chronic illnesses, and children who suffered from any condition likely to affect their protein metabolism or growth were excluded from the study. From a total of 313 invited subjects, 30 agreed to participate, and 28 were eligible for the study. Of the 15 boys who were the first to agree to participate in the study, 14 were eligible and 12 completed the intervention with milk, and of the remaining 15 boys, 14 were eligible and 12 completed the intervention with meat. All participants were Caucasian. Subjects and their parents received oral and written information about the study, and the parents gave their written consent. The children were examined at baseline and after 7 days of intervention.

Height was determined to nearest 1 mm using a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg using an electronic digital scale. Subjects wore only underpants when weighed.

Blood samples were drawn from a venipuncture after an overnight fast. Serum urea nitrogen (SUN) and serum glucose were determined colorimetrically (Vitros 950, Rocheste, NY, USA). Amino acids were determined by HPLC as described by Barkholt and Jensen (1989) with the exception that A-buffer had pH = 3.17 in order to separate citrulline and glutamic acid. Serum insulin and C-peptide was determined with solid phase, two-site fluoroimmunometric assays (AutoDELFIA, PerkinElmer, Turku, Finland).

An index of insulin resistance was obtained by using the HOMA for calculating relative insulin resistance and beta cell function (Matthews *et al*, 1985):

$$\text{Relative insulin resistance} = \text{glucose(mmol/l)} \times \text{insulin (pmol/l)}/135$$

$$\text{Beta cell function} = 3\tfrac{1}{3}\,\text{insulin(pmol/l)}/(\text{glucose (mmol/l)} - 3.5)$$

A disposition index was calculated as beta cell function/relative insulin resistance.

The participants (with their parents) kept a 3-day weighed food record prior to the intervention (Day −3 to −1) and during the last 3 days of the intervention (Day 4–7). The importance of maintaining usual dietary intake during the first 3-day period was emphasized to the children and parents. Average daily intakes of energy and nutrients were calculated for each subject by using a national food-composition database (DANKOST 2000, Dansk Catering Center, Herlev, Denmark).

The study was conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983. The Ethics Committee of Copenhagen and Frederiksberg approved the study (J. No. KF 01-097/00).

Statistics

Statistical analyses were performed with SPSS (version 11. 0; SPSS Inc. Chicago, IL, USA). All descriptive results are expressed as means ± s.d. Differences in the variables between the milk-group and the meat-group were determined by two-tailed unpaired Student's *t*-tests. Differences in the variables between baseline and after 7 days were determined by two-tailed paired Student's *t*-tests. Level of significance was set to 0.05 in all statistical procedures.

Results

Table 1 presents anthropometrical variables at baseline. There were no significant differences between the two

groups at baseline, except for age. The children in the milk-group gained on average 550 g of weight during the intervention.

There were differences in the composition of the habitual diet (baseline values) in the two groups (Table 2). The meat-group had a higher proportion of their energy from carbohydrate and a lower proportion from fat than the milk-group. The protein energy percentage (PE%) increased significantly in both groups. In the milk-group, the increase was 61%, and in the meat-group 54%. However, in the milk-group, the increased PE% was accompanied by a decrease in fat energy percentage, whereas in the meat-group, the increase in PE% was accompanied by a decrease in carbohydrate energy percentage. Furthermore, the energy intake increased after 7 days of intervention by 13% in the milk-group, whereas there was only a 3% nonsignificant increase in the meat-group.

In both groups, the increased protein intake resulted in similar increases in SUN, which is considered a valuable indicator of recent protein intake (Fomon, 1993) (Table 3). The sum of the BCAAs increased similarly in both groups ($P=0.184$), as did the sum of the insulinogenic amino acids (IAAs, BCAAs + arginine) ($P=0.217$).

In the milk-group, fasting insulin concentrations and relative insulin resistance increased significantly by 103 and 75%, respectively. However, in the meat-group, there was no increase in fasting insulin ($P=0.62$) or relative insulin resistance ($P=0.88$). Beta cell function increased significantly in both groups by 86% (milk-group) and 42% (meat-group), and C-peptide increased significantly by 26% in the milk-group, and nonsignificantly by 8.5% in the meat-group ($P=0.07$). Concentration of fasting glucose did not change in the milk-group ($P=0.49$), whereas it decreased significantly in the meat-group ($P=0.008$). The disposition index increased in the meat-group by 36%, and not in the milk-group ($P=0.38$). The ratio of insulin/C-peptide increased by 37% in the milk-group, whereas there was no increase in the meat-group ($P=0.92$).

Table 1 Description of anthropometrical variables of the milk-group and the meat-group at baseline[a]

	Milk-group (n = *12*)	*Meat-group* (n = *12*)
Age (y)	7.9 ± 0.07	8.3 ± 0.07[b]
Height (cm)	131.1 ± 5.8	131.9 ± 5.8
Weight (kg)	29.4 ± 5.1	29.0 ± 4.2
BMI (kg/m^2)	17.0 ± 1.9	16.6 ± 1.2

[a]Mean ± s.d.
[b]Different from milk-group; $P<0.001$.

Discussion

A high intake of milk more than doubled fasting serum insulin concentrations, which caused the relative insulin resistance to increase similarly, as there was no increase in fasting glucose. In the meat-group, however, there was no increase in insulin and insulin resistance. As the concentrations of BCAAs and IAAs increased similarly in the two groups, our results do not support that insulin secretion was stimulated through the BCAAs and arginine.

Our study was different from other studies addressing the same topic in a number of ways. We used a very high amount of animal protein, because we over a short period wanted to see if there was an effect or not. However, even if the protein intake during the intervention was quite high, about 4 g/kg body weight, many infants and young children have a protein intake at this level or higher (Rolland-Cachera *et al*, 1999). Furthermore, the high milk intake in the milk-group, about 2 l/day, equals an intake of 700 ml in a 10-kg infant, when calculated per kg body weight. Many infants have an intake at this level. We used the same amount of animal protein for the intervention in the two groups, which gives us more strength to evaluate the effect of protein quality. Furthermore, we have determined fasting levels of insulin and glucose, which are different from postprandial blood

Table 2 Description of the diet of the milk-group and the meat-group at baseline and after 7 days of intervention[a]

	Milk-group (n = *12*)		*Meat-group* (n = *12*)	
	Baseline	*Day 7*	*Baseline*	*Day 7*
Energy (MJ/day)	9.02 ± 1.56	10.16 ± 1.85[b]	8.93 ± 1.51	9.18 ± 2.00
Carbohydrate (E%)	51.4 ± 3.57	51.9 ± 4.08	56.6 ± 4.65[c]	46.7 ± 7.94[d]
Fat (E%)	34.6 ± 3.96	26.7 ± 4.10[d]	29.9 ± 4.56[e]	32.4 ± 5.37
Protein (E%)	13.1 ± 2.09	20.6 ± 1.67[d]	12.7 ± 0.76	19.9 ± 3.37[d]
Protein (g/day)	68.6 ± 9.95	121.4 ± 17.2[d]	65.3 ± 11.4	105.6 ± 33.8[f]
Milk (g/day)	416 ± 206	2024 ± 44[d]	356 ± 155	236 ± 160
Meat (g/day)	90.3 ± 34.0	82.1 ± 25.5	81.5 ± 42.7	291 ± 118[d]

[a]Mean ± s.d.
[b]Different from baseline; $P<0.01$.
[c]Different from baseline in milk-group; $P<0.01$.
[d]Different from baseline; $P<0.0001$.
[e]Different from baseline in milk-group; $P<0.05$.
[f]Different from baseline; $P<0.001$.

Table 3 Description of biochemical parameters of the milk-group and the meat-group at baseline and after 7 days of intervention[a]

	Milk-group (n = *12*)		*Meat-group* (n = *12*)	
	Baseline	*Day 7*	*Baseline*	*Day 7*
SUN (mmol/l)	4.72 ± 1.06	6.63 ± 0.71[b]	4.85 ± 0.75	6.55 ± 1.51[c]
∑ BCAA (pmol/μl)	173 ± 29	227 ± 20[b]	188 ± 32	221 ± 43[d]
∑ IAA (pmol/μl)	210 ± 29	260 ± 22[b]	221 ± 33	249 ± 41[d]
Valine (pmol/μl)	100 ± 19	139 ± 14[b]	107 ± 19	129 ± 29[d]
Isoleucine (pmol/μl)	24 ± 3.2	29 ± 2.4[e]	27 ± 5.7	31 ± 5.8
Leucine (pmol/μl)	50 ± 7.6	59 ± 5.7[e]	53 ± 8.9	61 ± 9.5[d]
Arginine (pmol/μl)	37 ± 4.1	32 ± 3.9[b]	34 ± 3.3[f]	28 ± 3.5[b]
C-peptide (pmol/l)	237.8 ± 52.5	299.4 ± 86.5[e]	250.4 ± 49.3	271.8 ± 48.3
Insulin (pmol/l)	22.4 ± 6.56	45.04 ± 25.8[c]	25.08 ± 9.05	26.73 ± 6.89
Glucose (mmol/l)	4.80 ± 0.30	4.72 ± 0.36	4.79 ± 0.30	4.54 ± 0.25[c]
Relative insulin resistance[g]	0.80 ± 0.28	1.40 ± 0.73[c]	0.90 ± 0.36	0.90 ± 0.24
Beta cell function[h]	57.96 ± 12.6	108.0 ± 38.1[c]	64.8 ± 17.0	88.98 ± 24.5[b]
Disposition Index[i]	76.59 ± 20.5	85.5 ± 27.0	78.2 ± 27.6	106.4 ± 31.6[d]
Insulin/C-peptide	0.094 ± 0.02	0.129 ± 0.03[b]	0.098 ± 0.02	0.099 ± 0.02

SUN, serum urea nitrogen; ∑ BCAA, sum of the branched chain amino acids (leucine + isoleucine + valine); ∑IAA, sum of the insulinogenic amino acids (BCAAs + arginine).
[a]Mean ± s.d.
[b]Different from baseline; $P<0.0001$.
[c]Different from baseline; $P<0.01$.
[d]Different from baseline; $P<0.05$.
[e]Different from baseline; $P<0.001$.
[f]Different from baseline in milk-group; $P<0.05$.
[g]Relative insulin resistance = glucose (mmol/l) × insulin (pmol/l)/135 (Matthews *et al*, 1985).
[h]Beta cell function = ($3\frac{1}{3}$ insulin (pmol/l))/(glucose (mmol/l) − 3.5) (Matthews *et al*, 1985).
[i]Disposition Index = Beta cell function/relative insulin resistance (Matthews *et al*, 1985).

samples. Thus, we believe that our study can give information that is helpful in understanding the interaction between diet and the glucose–insulin metabolism.

The study has some limitations. We used the HOMA to determine insulin resistance and beta cell function from fasting concentrations of insulin and glucose. The HOMA is not the best method to determine neither secretion nor effect of insulin in comparison to, for example, oral glucose tolerance test or a clamp test. However, the HOMA estimates correlate significantly with independent measures of beta cell function and insulin resistance in normal and diabetic subjects (Matthews *et al*, 1985).

By chance, there were significant differences in fat and carbohydrate content of the diet at baseline between the two groups. However, intakes of protein, meat and milk were not statistically different at baseline. Also, except for the intervention with meat and milk, the diet was not controlled. This resulted in some minor but significant differences in dietary intake between the two groups. Most important was that during the intervention, the energy intake increased by 13% in the milk-group, but remained at the same level in the meat-group. This could be due to the fact that satiety is better regulated in relation to solid than to liquid energy providers (DiMeglio & Mattes, 2000).

We cannot conclude from our results whether the hyperinsulinemia has induced the insulin resistance or whether the insulin resistance is being compensated by an increased insulin secretion in the milk-group. The conventional understanding is that hyperinsulinemia, which is seen at insulin resistance and not at least at NIDDM, is a secondary phenomenon to insulin resistance (DeFronzo, 1988; DeFronzo *et al*, 1992; Swinburn *et al*, 1995). However, results from some studies indicate the opposite allegation, that is, that increased insulin secretion and/or hyperinsulinemia in some conditions may precede and actually be the cause of insulin resistance (Rizza *et al*, 1985; Del Prato *et al*, 1994; Le Stunff & Bougneres, 1994). The fact that plasma glucose concentration did not increase in the milk-group at the same time as did the insulin — and in fact decreased after 1 week with a high intake of meat — indicate that the hyperinsulinemia is primary. The increase of the disposition index in the milk-group, however nonsignificant, also indicates that the hypersecretion of insulin is primary. However, this could be an indirect indication that intake of milk — as opposite to meat — induces insulin resistance as a primary phenomenon, and that the hyperinsulinemia induced by a high intake of meat did not at the same time induce insulin resistance. This could though be a question of dose.

An increase in fasting concentration of insulin may be caused by a decrease in insulin clearance, with an unchanged insulin secretion. However, the significant increase in plasma C-peptide concentration supports an increase in the endogen insulin secretion. But the increase in the ratio of

insulin to C-peptide suggests a simultaneous decreased insulin clearance, which to some degree contributes to the hyperinsulinemia, but importantly, does not explain the hyperinsulinemia completely. The decreased insulin clearance may again be secondary to the insulin resistance. Overall, our results suggest therefore, that hyperinsulinemia is a primary phenomenon to insulin resistance.

Since the concentrations of BCAAs and IAAs increased similarly in the two groups, our results do not support that insulin secretion was stimulated through the BCAAs and arginine. Although we find it most likely that the effects on insulin concentration in the milk-group were caused by an increased intake of certain amino acids or functional peptides, we cannot exclude that the higher energy intake, the increased body weight or the change in macronutrient composition of the diet had an effect. Also, we cannot exclude, that there are some factors in meat that inhibit the effect of protein on insulin and insulin resistance. The observed effect might be from simple carbohydrates in the milk. However, from a study based on regular or fermented milk products, where a discrepancy between glycemic index and insulinemic index was found, it was concluded that the insulinotrophic effect was not related only to the carbohydrate component of milk, but also to some yet unidentified food component (Ostman *et al*, 2001).

The increased concentrations of IGF-I (209–249 ng/ml, $P<0.001$) and IGFBP-3 (3612–3806 ng/ml, $P<0.05$), which was also observed in the milk-group in this study (Hoppe *et al*, 2004) might be explained by the hyperinsulinemia after intervention with milk. Some data suggest that insulin stimulates the hepatic IGF-I production in young subjects with type I diabetes (Amiel *et al*, 1984), in diabetic rats (Olchovsky *et al*, 1990) and in rat hepatocytes (Johnson *et al*, 1989), whereas plasma concentration of IGF-I decreased slightly during an intravenous glucose tolerance test (Nyomba *et al*, 1997). Also, in short-statured normal 9-y-old children, IGF-I and IGFBP-3 were associated with insulin resistance, as calculated by HOMA (Bleicher *et al*, 2002).

Even if it is well known that hyperinsulinemia and insulin resistance antedates the development of NIDDM (DeFronzo *et al*, 1992) in adults and in overweight children, we cannot conclude from one short-term intervention study in prepubertal healthy children that high intakes of milk increase the risk of developing NIDDM. In fact, one could speculate that the hyperinsulinemia and the insulin resistance in this phase of development and growth are protective. The hormonal response, including insulin, to a meal is different in breast-fed and formula-fed term infants (Lucas *et al*, 1980), and breast-feeding seems to protect against both overweight (Dewey, 2003) and NIDDM (Schrezenmeir & Jagla, 2000). Also, insulin is an anabolic factor involved in growth, and increased insulin concentration might be beneficial in children during growth, and it might certainly have different implications in children and adults.

The effect of high protein intakes from different sources on glucose–insulin metabolism needs to be studied further, and the mechanism for the insulinotrophic effect of milk is not known, and the potential long-term metabolic consequences need to be further elucidated.

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