Low Fasting Triglycerides: Hallmark of the Healthy Large Hip?

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Body fat distribution modulates risk for type 2 diabetes mellitus. We evaluated potentially involved metabolic risk factors. In a population of 282 male and 157 female healthy subjects (data from the San Antonio and the European Group of Insulin Resistance (EGIR) study cohorts), we evaluated associations between body fat distribution (assessed by waist and hip circumference) and parameters of lipid- and glucose metabolism, including clamp measurements of insulin sensitivity. After stratification for BMI, fasting triglycerides were lower in the presence of a large hip, and higher in a large waist. Persons with the largest BMI (3rd tertile) showed a difference in triglyceride levels of 1.5 vs. 2.4 mmol/l in large vs. small hip circumference groups ($P < 0.038$), and a difference of 1.5 vs. 1.2 mmol/l in large vs. small waist circumference groups ($P < 0.025$). A similar analysis did not reveal a difference in insulin sensitivity. Linear regression analyses confirmed the findings; they revealed negative associations between triglycerides and hip, and (for women borderline statistically significant) positive associations between triglycerides and waist, after adjustment for BMI, mutual confounding, and age (β ± s.e.; men: –0.48 ± 0.005, $P < 0.001$, and 0.21 ± 0.005, $P < 0.05$; women: –0.78 ± 0.007, $P < 0.001$, and 0.24 ± 0.005, $P < 0.065$), respectively. Linear regression analyses revealed similar opposite associations with high-density lipoprotein (HDL)-cholesterol, though not with glucose, insulin, or insulin sensitivity as measured with the clamp method. In our study population of healthy persons, body fat distribution is associated with fasting triglycerides and HDL-cholesterol, and not with insulin sensitivity. Metabolic risk of unfavorable body fat distribution may be modulated by lower triglyceride storage capacity.

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INTRODUCTION

Obesity increases risk for cardiovascular disease and diabetes mellitus, but the increase in risk is not linear with the BMI. So called android obesity (apple shape) has a remarkably different risk than gynoid obesity (pear shape). Apparently, distribution of fat modulates risk. Abdominal obesity, clinically assessed by the "waist circumference," is strongly associated with cardiovascular disease and diabetes mellitus (1–3), whereas "hip circumference" appeared to be protective (4). The waist circumference is regarded as the central feature of the metabolic syndrome (International Diabetes Federation 2005 criteria), which together with hypertension, lipid disturbances (increased triglycerides and decreased high-density lipoprotein (HDL)-cholesterol), and impaired fasting glucose (feature of insulin resistance), precedes type 2 diabetes mellitus and cardiovascular disease (5,6). In contrast, the hip circumference is associated with a decreased incidence in cardiovascular disease (7,8), diabetes mellitus (9,10), and might even predict health and longevity, especially in women (4).

Because diabetes mellitus is preceded by insulin resistance and lipid disturbances, we evaluated associations between body fat distribution (assessed by waist and hip circumference) and components of glucose metabolism, including clamp measurements of insulin sensitivity, triglyceride concentrations, and HDL-cholesterol.

METHODS AND PROCEDURES

We analyzed data from the European Group of Insulin Resistance (EGIR) database (which comprises nondiabetic Caucasian Europeans) and the San Antonio Metabolism Study cohort (which includes non-Hispanic white Caucasian, and Hispanic residents of San Antonio, TX), including measurements of insulin sensitivity obtained with the use of the euglycemic insulin clamp technique (with an infusion rate of 240 pmol/min/m for 2 h). Details on the study cohort, the protocol, experimental and analytical methods have been published previously (11–16). Approval of the protocol by the local Ethics Committee and informed consent from all subjects was obtained before the studies at each geographical centre. For the purpose of the present study, insulin sensitivity was taken to be the steady-state total body insulin-mediated glucose disposal rate (M_{LBM}), expressed as μmol per min per kg of fat-free (or lean body) mass (μmol/min/kg/lbm). Blood samples were collected in the fasting state for the measurement of fasting plasma glucose, fasting plasma insulin, fasting plasma triglyceride, and HDL-cholesterol. Plasma glucose was measured by the glucose oxidase method. Plasma insulin concentrations were measured by radioimmunoassay. Serum lipid levels were

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assayed by standard enzymatic assays. Fat mass (hence lean body mass) was measured by different techniques: underwater weighing, electrical bio-impedance, and tracer water. The results were generally in agreement, but for homogeneity it was decided to use the sex-specific Hume's formula throughout.

For the purpose of the present study, subjects without diabetes or impaired glucose tolerance were selected on basis of the availability of the anthropometric parameters BMI, waist, hip circumference, and insulin sensitivity; the steady-state total body insulin-mediated glucose disposal rate (M), expressed as μmol per min per kg of fat-free mass (μmol/min/kg lean body mass). Only subjects with complete data were analyzed ($n = 439$). Noneligible subjects of the database were in general younger and had a slightly lower BMI.

Statistical analyses

Data are given as means (± s.d.) or medians and their range, if distributions were skewed. Distributions of BMI, hip and waist circumference were divided into tertiles to provide insight into their mutual relationships and their relationship with insulin sensitivity and triglycerides, with the help of 3D graphs. Cut-points were calculated for male and female subjects separately, and the tertile-groups combined afterwards, to improve statistical power. Cut-points were 101 and 112 cm for hip circumference in female subjects (tertile-groups; lowest through 101, 101 through 112, 112 through highest), 99 and 104 cm for hip circumference in male subjects, 86 and 96 cm for waist circumference in female subjects, 90 and 98 cm for waist circumference in male subjects, 26 and 31 kg/m^2 for BMI in female subjects, and 25 and 28 kg/m^2 for BMI in male subjects. Differences between groups were analyzed by means of the Mann–Whitney U-test.

Linear regression analysis was applied to adjust for mutual confounding (hip and waist circumference), BMI, and age. Results were expressed as standardized coefficients (β) and R^2, the proportion of variation "explained" by the independent variables. If appropriate, distributions were transformed into their natural logarithm to fulfill assumption criteria. A P value <0.05 was regarded statistically significant. Analyses were performed with the SPSS-PC software package, version 11.0.1 (SPSS, Chicago, IL).

RESULTS

Table 1 shows population characteristics of 157 women and 282 men, selected from the EGIR and San Antonio study cohorts. The subjects had a wide range in age, BMI, waist and hip circumference. Data were provided in means (± s.d.) or median values and ranges, if distributions were skewed. Except for 44 Hispanics, subjects were Caucasians. Performing the analyses without the Hispanic population did not essentially change the results. Two women and 13 men had triglyceride concentrations >5.6 mmol/l and were excluded from analyses concerning triglycerides, though inclusion did not essentially change the results (data not shown). Triglyceride levels >5.6 mmol/l are clinically regarded as very high, and might be caused by specific lipid disorders (6). Table 1 showed further a wide range in BMI; performing analyses without subjects with a BMI >40 kg/m^2 did also not essentially change the results (data not shown).

Figure 1 shows that waist and hip circumference were strongly associated with BMI. BMI is lowest in subjects with a small hip and small waist circumference (1st tertile of both; 23 kg/m^2) as compared to small waist (1st tertile) and large hip circumference (3rd tertile; 29 kg/m^2, $P < 0.001$), or small hip (1st tertile) and large waist circumference (3rd tertile; 27 kg/m^2, $P < 0.001$), etc. In the following analyses, all tertiles of BMI, waist and hip circumference were calculated separately for male and female subjects (see Methods and Procedures), and afterwards combined to improve statistical power.

In healthy subjects with a large BMI (3rd tertile), fasting triglyceride concentrations appeared to be lower in the presence of a large hip as compared to a small hip circumference (3rd vs. 1st tertile; 1.5 vs. 2.4 mmol/l, $P < 0.038$; Figure 2a). And, in subjects with similar BMI (3rd tertile), fasting triglyceride concentrations were higher in the presence of a large waist circumference vs. a small waist circumference (3rd vs. 1st tertile; 1.5 vs. 1.2 mmol/l, $P < 0.025$, Figure 2b).

A similar analysis with respect to insulin sensitivity (clamp method), fasting glucose, fasting insulin, or HDL-cholesterol could not reveal such divergent associations of body fat

Table 1 Study population characteristics, anthropometric measurements and biochemistry

	Women	Men
N	157	282
Caucasian	129	266
Hispanic	28	16
Age (years)	41 (33–53)	50 (35–65)
BMI (kg/m^2)	28.9 ± 6.2	27.1 ± 4.8
Waist circumference (cm)	92 ± 15	95 ± 12
Hip circumference (cm)	108 ± 12	103 ± 11
Fasting plasma glucose (mmol/l)	5.0 ± 0.5	5.1 ± 0.5
Fasting plasma insulin (pmol/l)	72 (55–115)	69 (46–96)
Insulin sensitivity (μmol/min/kg lean body mass)	40.9 (31.1–55.0)	45.9 (34.1–58.8)
Triglycerides (mmol/l)[a]	1.10 (0.77–1.5)	1.39 (1.0–2.0)
HDL-cholesterol (mmol/l)	1.3 ± 0.4	1.10 ± 0.4
Systolic blood pressure (mm Hg)	125 (113–140)	124 (115–140)
Diastolic blood pressure (mm Hg)	82 (75–90)	81 (74–90)

Data are numbers, mean values ± s.d. or median values (interquartile ranges). HDL, high-density lipoprotein.
[a]Two women and 13 men had fasting triglyceride concentrations >5.6 mmol/l and were excluded from analyses containing triglycerides.

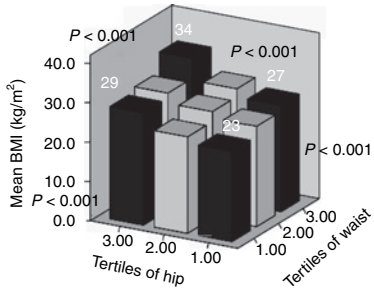

Figure 1 Associations between BMI, hip and waist circumference in healthy subjects. BMI is lowest in subjects with a small hip and waist circumference (1st tertile of both; 23 kg/m^2) as compared to small waist (1st tertile) and large hip circumference (3rd tertile; 29 kg/m^2, $P < 0.001$) or small hip (1st tertile) and large waist circumference (3rd tertile; 27 kg/m^2, $P < 0.001$). (BMI, hip and waist tertiles were calculated for male and female subjects separately).

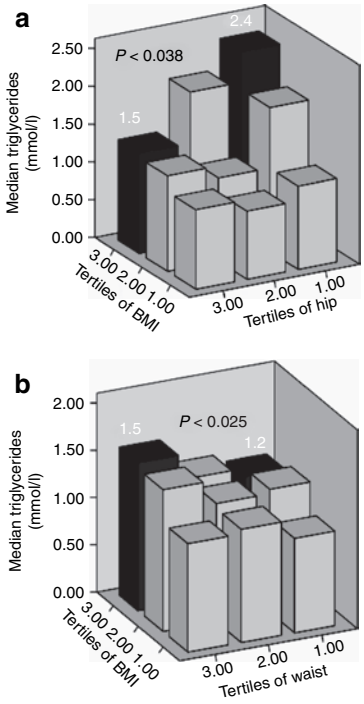

Figure 2 Body fat distribution and triglycerides. (**a**) Association between triglycerides and hip circumference in healthy subjects. Triglyceride concentrations are lower in subjects with a large hip circumference (3rd tertile; 1.5 mmol/l) as compared to subjects with a small hip circumference (1st tertile; 2.4 mmol/l, $P < 0.038$), after stratification for BMI (hip and BMI tertiles were calculated for male and female subjects separately). (**b**) Association between triglycerides and waist circumference in healthy subjects. Triglyceride concentrations are higher in subjects with a large waist circumference (3rd tertile; 1.5 mmol/l) as compared to subjects with a small waist circumference (1st tertile; 1.2 mmol/l, $P < 0.025$), after stratification for BMI. (Waist and BMI tertiles were calculated for male and female subjects separately).

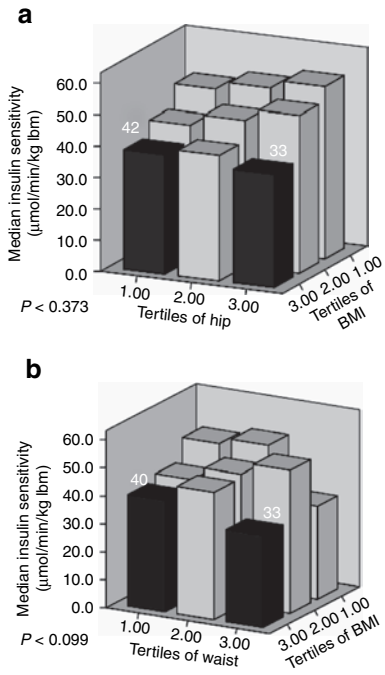

Figure 3 Body fat distribution and insulin sensitivity (clamp). (**a**) Association between insulin sensitivity and hip circumference in healthy subjects. A statistically significant difference in insulin sensitivity (clamp) could not be established between subjects with a small hip circumference (1st tertile; 42 µmol/min/kg lbm) as compared to subjects with a large hip circumference (3rd tertile; 33 µmol/min/kg lbm, $P < 0.373$), in the presence of a large BMI (3rd tertile). (Hip and BMI tertiles were calculated for male and female subjects separately). (**b**) Association between insulin sensitivity and waist circumference in healthy subjects. A statistically significant difference in insulin sensitivity (clamp) could not be established between subjects with a small waist circumference (1st tertile; 40 µmol/min/kg lbm) as compared to subjects with a large waist circumference (3rd tertile; 33 µmol/min/kg lbm, $P < 0.099$), in the presence of a large BMI (3rd tertile) (Waist and BMI tertiles were calculated for male and female subjects separately).

distribution (data not shown, except for insulin sensitivity), i.e., in healthy subjects having a large BMI (3rd tertile), insulin sensitivity was not statistically different comparing a small hip circumference vs. a large hip circumference (1st vs. 3rd tertile; 42 vs. 33 µmol/min/kg lbm, $P < 0.373$; **Figure 3a**), also insulin sensitivity was not statistically different comparing a small waist circumference vs. a large waist circumference (1st vs. 3rd tertile; 40 vs. 33 µmol/min/kg lbm, $P < 0.099$; **Figure 3b**).

The divergent association of fasting triglyceride concentrations and body fat distribution was confirmed by use of linear regression analyses, allowing adjustment for BMI, mutual confounding (hip and waist circumference) and age. Analyses were performed for women and men separately, because body fat distribution generally shows distinct gender differences. Women showed an inverse association between fasting triglyceride concentrations and hip circumference ($\beta \pm$ s.e.: -0.78 ± 0.007, $P < 0.001$), and a (borderline statistically significant) positive association between fasting triglycerides and waist circumference ($\beta \pm$ s.e.: 0.24 ± 0.005, $P < 0.065$), after adjustment for BMI, mutual confounding, and age (**Table 2**). Similarly, men showed an inverse association between fasting triglyceride concentrations and hip circumference ($\beta \pm$ s.e.: -0.48 ± 0.005, $P < 0.001$), and a positive association between fasting triglycerides and waist circumference ($\beta \pm$ s.e.: 0.21 ± 0.005, $P < 0.05$), after adjustment for BMI, mutual confounding, and age.

Linear regression analyses did also reveal a divergent association between HDL-cholesterol and body fat distribution. Women showed a positive association between HDL-cholesterol and hip circumference ($\beta \pm$ s.e.: 0.39 ± 0.005, $P < 0.05$), and an inverse association between HDL-cholesterol and waist circumference ($\beta \pm$ s.e.: -0.35 ± 0.004, $P < 0.01$), after adjustment for mutual confounding, age, and BMI. Similarly, men showed a positive association between HDL-cholesterol and hip circumference ($\beta \pm$ s.e.: 0.36 ± 0.004, $P < 0.001$), and an inverse association between HDL-cholesterol and waist circumference ($\beta \pm$ s.e.: -0.32 ± 0.004, $P < 0.001$), after adjustment for mutual confounding, age, and BMI (**Table 2**).

Linear regression analyses, separated for women and men, did not reveal an association between insulin sensitivity and body fat distribution, though positive associations were shown in women for fasting glucose concentrations and waist circumference ($\beta \pm$ s.e.: 0.51 ± 0.005, $P < 0.001$), and positive associations

Table 2 Independent contributions of waist and hip circumference to components of lipid and glucose metabolism

	Hip circumference (β ± s.e.)	Waist circumference (β ± s.e)	R^2 of model[a] (%)
Fasting triglycerides			
Women	−0.78 ± 0.007*	0.24 ± 0.005	30
Men	−0.48 ± 0.005*	0.21 ± 0.005***	19
HDL-cholesterol			
Women	0.39 ± 0.005***	−0.35 ± 0.004**	28
Men	0.36 ± 0.004*	−0.32 ± 0.004**	11
Insulin sensitivity (clamp)			
Women	0.33 ± 0.006	−0.12 ± 0.004	17
Men	0.15 ± 0.004	−0.12 ± 0.004	18
Fasting glucose			
Women	−0.15 ± 0.007	0.51 ± 0.005*	8
Men	0.03 ± 0.005	−0.13 ± 0.005	9
Fasting insulin			
Women	0.29 ± 0.008	0.28 ± 0.005***	32
Men	−0.01 ± 0.005	0.21 ± 0.004***	31

Adjusted for mutual confounding (hip or waist circumference), age, and BMI.
HDL, high-density lipoprotein.
[a]Proportion of variance "explained" by the model, including BMI, waist and hip circumferences and age.
*$P < 0.001$. **$P < 0.01$. ***$P < 0.05$.

were also shown for fasting insulin and waist circumference in women (β ± s.e.: 0.28 ± 0.005, $P < 0.05$), and men (β ± s.e.: 0.21 ± 0.004, $P < 0.05$) (Table 2). Replacement of BMI-linear by BMI-categorized showed essentially similar opposite associations for triglycerides and HDL-cholesterol, whereas it did not reveal opposite associations for glucose, insulin, or insulin sensitivity with body fat distribution. Furthermore, subanalyses of the European Group of Insulin Resistance (EGIR) database vs. the San Antonio Metabolism Study cohort did not essentially change the results, apart from loss of statistical power.

Repeating linear regression analyses, with combined data of men and women, did reveal a positive association between insulin sensitivity and hip circumference, though no statistically significant ($P < 0.05$) association with waist circumference, after adjustment for BMI, mutual confounding (hip and waist circumference), age, and gender. Further exploration, by evaluating effect modification in this model, revealed a statistically significant interaction between BMI and age on insulin sensitivity, which, however, did not essentially change the associations between hip and waist circumference and insulin sensitivity (data not shown). Yet, the variation (R^2) of insulin sensitivity explained by hip circumference in these models was at maximum 1%. Replacement of insulin sensitivity by triglycerides in this model including the combined data of men and women, confirmed the findings of the separate analyses as provided in Table 2, and showed a highly significant inverse association between triglycerides and hip circumference, as well as a highly significant positive association between triglycerides and waist circumference. The variation (R^2) of triglycerides explained by hip circumference was 9.5% and by waist circumference 6.5% (data not shown). Evaluation of effect modification between BMI and age in the latter model was not statistically significant. Evaluation of effect modification between BMI and hip or waist circumference, which might be suspected by the analyses depicted in Figure 2, was also not statistically significant (data not shown).

DISCUSSION

We report here on a link between fasting triglyceride concentrations and body fat distribution in healthy persons. In persons generally regarded as having increased metabolic risk; the ones with a large BMI, triglyceride concentrations were lower in the presence of a large thigh (hip circumference), and higher in the presence of a large waist. The study is one of the first studies in humans to suggest, without proving, that adipocyte dysfunction precedes deterioration of muscle insulin sensitivity in obesity-related metabolic disturbances. The finding suggests a difference in triglyceride storage capacity between thigh and abdominal fat. This capacity to adequately store triglycerides may modulate the beneficial effects of gynoid obesity, and seems to play a more principal role than insulin sensitivity, in view of the fact that we did not find a link with insulin sensitivity in these healthy subjects, despite the use of the "gold standard method" to assess insulin sensitivity (17).

Thigh fat may contain adipose tissue better capable of buffering lipid-excess than abdominal fat (18). Recently, it was shown that women with a large thigh more efficiently stored their meal fat than women with a large amount of visceral fat (19). Maassen *et al.* anticipated that the buffering function of adipose tissue may depend on number and activity of mitochondria within adipocytes, contributing to the threshold at which fatty acids are released into the circulation, and, if deficient, leading to insulin resistance and type 2 diabetes mellitus (20,21). Preferential partitioning of lipid-excess into gluteal–femoral fat may directly affect glucose metabolism by reducing harmful effects of circulating free fatty acids on the ability of insulin to suppress hepatic glucose production (22), and it may also protect endothelial function (23).

The present analyses also revealed opposite associations between HDL-cholesterol and body fat distribution, after adjustment for confounding. Again, a large thigh was associated with favorable HDL-cholesterol concentrations whereas a large waist was associated with low cholesterol concentrations. HDL-cholesterol appears to play an important role with respect to the development of type 2 diabetes mellitus as well as cardiovascular disease (24,25). Triglycerides and HDL-cholesterol are inversely associated, though triglycerides may more clearly explain their contribution to the development of metabolic disturbances (26).

The findings on triglyceride- and HDL levels are somehow in agreement with former reports, though the absence of a statistically significant opposite association between insulin sensitivity and body fat distribution in the same persons with similar analytic techniques makes the present study distinctive (27–30). Of course, if more persons had been included in

the study opposite associations with insulin sensitivity could have been revealed, though the finding that opposite associations with triglycerides are far stronger and already detectable in simple stratified analyses (**Figure 2**), as well as the fact that 16% of variation in triglycerides (R^2) was explained by hip and waist circumference vs. at maximum 1% of variation of insulin sensitivity (R^2) by hip circumference alone (in linear regression models), supports a primary role for triglycerides in the metabolic risk difference between hip and waist circumference, and is in line with a recent prospective study in healthy young men, reporting prediction of diabetes by an increase in triglyceride level over time (31). Other studies on the topic showed variable findings. One study showed favorable associations between leg fat and parameters of insulin resistance, as calculated by values of glucose and insulin after an oral glucose tolerance test (28). Another study showed a positive association between lower-body fat mass and insulin sensitivity as estimated by the Matsudas index; they concluded that this effect could partly be explained by variations in serum adiponectin levels (29). They reported also lower serum insulin in a subgroup of men selected for large lower-body fat mass concentration as compared to a subgroup of men selected with small lower-body fat mass, matched for trunkal fat mass. Given that we used most precise measurements of insulin sensitivity in a healthy population (17), the better associations with triglycerides and HDL-cholesterol as compared to insulin sensitivity suggest an initial disturbance of lipid metabolism, which partly depend on body fat distribution, though longitudinal studies are required to find out whether disturbances in lipid metabolism precede insulin resistance. Thus, part of the discrepancy might be explained by different techniques to assess insulin sensitivity and by different study-populations, with consequently different stages in the pathogenic pathway. One study was performed in healthy postmenopausal women (28), and another in randomly selected men in combination with juvenile onset obese men (29). Two large studies showed opposite effects on triglycerides and HDL-cholesterol of waist vs. hip circumference in agreement with our results (27,30), though both studies showed also consistently opposite effects on glucose and insulin. One of these studies included patients with diabetes (27), and the other study included subjects with impaired glucose tolerance (30). Consequently, the range of glucose and insulin is much larger in these populations than in our healthy population (without diabetes and impaired glucose tolerance), which facilitates detection of an association. The absence of an opposite association of insulin sensitivity with body fat distribution in the present study might therefore be even more intriguing, because the range in insulin sensitivity is large in the present healthy study population (11).

Definite conclusions cannot be made with respect to causal interference, because most of the available data are cross-sectional (27–30), and measurements of one prospective study are limited (31). It is further not completely clear whether the association between the lipids and body fat distribution is linear or more explicit in subjects with a large BMI; further studies in large healthy populations are needed. Another potential limitation of the present study is that hip circumference was not separated into peripheral muscle, fat masses, and pelvic size, because peripheral muscle atrophy might influence insulin sensitivity (32). Small differences between women and men have not been evaluated; they might be explained by regional differences in adipocyte metabolism with respect to lipoprotein lipase activity and lipolysis, or different effects of adrenal hormones and sex steroids (33).

In conclusion, hip and waist circumference show divergent effects with respect to fasting triglycerides and HDL-cholesterol. The findings support a protective role by gynoid adiposity through better triglyceride storage capacity, preventing harmful lipid exposure.

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DISCLOSURE

The authors declared no conflict of interest.

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