Gender Differences in the Development of Hyperlipemia and Atherosclerosis in Hybrid Hamsters

Sander J. Robins, Joan M. Fasulo, George M. Patton, Ernst J. Schaefer, Donald E. Smith, and Jose M. Ordovas

In response to a diet enriched in saturated fat and cholesterol (CH), male Syrian hamsters develop hyperlipemia and changes of early atherosclerosis. However, it has not been determined if female hamsters are equally susceptible to an atherogenic diet. Male and female hamsters of the F_1B hybrid strain (Bio Breeders, Fitchburg, MA) were fed either a chow diet or this diet (HiFat) with added saturated fat (10% coconut oil) and CH (0.05%) for up to 12 weeks. Female hamsters ate significantly more than males, and with the HiFat diet gained threefold more weight than males. However, with the HiFat diet, serum triglycerides (TGs) and CH were markedly increased only in male hamsters. Furthermore, only in males was there a significant increase in stainable fat in the aorta that corresponded to an increase in subintimal foam cells. In freely feeding males, the largest percentage increase in serum CH was in the TG-rich fraction of lipoproteins. After females were castrated, serum TG and CH levels increased to the same extent as in males. These studies demonstrate a profound gender difference in response to an atherogenic diet in these hamsters that has parallels to the lipid patterns of humans and their susceptibility to atherosclerosis.

THERE ARE STRIKING differences between males and females in the development of atherosclerosis and coronary heart disease, which in great part can be attributed to differences in plasma lipids. A wide variety of animals have been used in atherosclerosis research in an attempt to simulate both lipid and vessel changes of atherosclerosis in response to a diet enriched in saturated fat and cholesterol (CH). Thus far, in only certain kinds of monkeys has an "atherogenic" diet been reported[1,2] to produce changes that resemble the human condition, in so far as males but not females develop characteristic vascular lesions in conjunction with lipid (or lipoprotein) abnormalities that are akin to changes in humans.

In recent years, the Syrian (Golden) hamster has been used with increasing frequency to study effects of dietary fat changes on plasma low-density lipoprotein (LDL) kinetics,[3-6] biliary lipid secretion,[7-9] and a number of aspects of hepatic lipid metabolism.[10-12] In response to a modest increase in dietary CH and saturated fat, Syrian hamsters develop a sizable increase in both serum triglycerides (TGs) and CH.[13,14] With this kind of diet, foam cells, the earliest characteristic lesion of atherosclerosis,[15] are found in the thoracic aorta in approximately 4 weeks.[13]

However, it is notable that all past studies of the response of hamsters to an increase in dietary fat appear to have been confined to male animals. It has not been determined if female hamsters have the same propensity as male hamsters to respond to an atherogenic diet with either serum lipid or vascular changes or, alternatively, show the same differences in response that have been well-established for male and female primates. To assess the effect of gender in response to an atherogenic diet in the hamster, the present study was performed using young hamsters of the F_1B strain, since it has been shown that males of this particular colony of hamsters are highly susceptible to hyperlipemia with a relatively modest increase in the amount of dietary saturated fat and CH,[16] that F_1B males respond to a saturated and unsaturated fat diet like humans,[17] and that in males morphologic changes consistent with atherosclerosis can be produced in a relatively short period.[16]

From the Department of Medicine, Veterans Administration Medical Center, Boston; Boston University School of Medicine, Boston; and US Department of Agriculture–Human Nutrition Research Center on Aging at Tufts University, Boston, MA.

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Address reprint requests to Sander J. Robins, MD, RB-8, Research Bldg, Boston VA Medical Center, 150 S Huntington Ave, Boston, MA 02130.

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MATERIALS AND METHODS

Animals

The protocol for this study was approved by the Animal Care and Use Committees of the Boston Veterans Administration Medical Center and US Department of Agriculture at Tufts University, and was undertaken in American Association for Accreditation of Laboratory Animal Care (AAALAC)-accredited facilities at both institutions. Male and female F_1B hamsters were obtained from Bio Breeders (Fitchburg, MA) at 8 weeks of age and maintained in a 12-hour light-cycle room (dark from 6 AM to 6 PM). One week after delivery, animals were divided into groups of two to four per cage and fed either a powdered chow diet (5001M; Ralston Purina, St Louis, MO) or this same chow diet enriched with 10% hydrogenated coconut oil (product #5240; Bio-Serv, Frenchtown, NJ) and 0.05% CH (HiFat). Fatty acid composition of the coconut oil was determined by high-performance liquid chromatography,[18] with only saturated fatty acids detected: 6:0 (1.0%), 8:0 (5.9%), 10:0 (6.7%), 12:0 (52.4%), 14:0 (18.4%), 16:0 (8.0%), and 18:0 (7.1%).

Animals were fed *ad libitum*, and blood was routinely obtained from freely feeding animals at the midpoint of the 12-hour dark cycle. In one separate group of animals, blood was obtained after animals had been fasted for 18 hours. For serial determinations of lipids, blood was obtained in approximately 400-μL amounts by retro-orbital puncture after anesthesia with the inhalant isoflurane. With repeated bleeding, hematocrits were routinely determined, and in no case were these values less than 45%. All surgery was undertaken using sodium pentobarbital 50 mg/kg intraperitoneal anesthesia. Ovariectomy was performed through a midline abdominal incision by doubly ligating each oviduct, dividing the oviduct between sutures, and then removing the ovaries. Sham ovariectomies were performed in a control group by opening the

abdomen and briefly manipulating the mesentery. After surgery, animals were allowed to recover for 1 week before being started on diets.

Aortas were obtained for morphology by perfusing the heart with 10% neutral buffered Formalin for 20 minutes at a pressure of 100 mm Hg. The heart was then removed together with the ascending and thoracic aorta. The section of aorta between the third cervical vessel and 1 mm distal to the aortic valve, measuring approximately 5 mm, was used to determine the area affected by lesion development.

Analytic Procedures

CH and TG levels in whole-serum and lipoprotein fractions were measured by automated enzymatic procedures using the Kodak DT 60 analyzer (Eastman Kodak, Rochester, NY). Ultracentrifugation of serum was simultaneously performed at two densities, 1.019 and 1.063 g/mL, to calculate (by subtraction from the total amounts of CH and TG in serum) the amount of CH and TG in the density fractions of less than 1.019, 1.019 to 1.063, and greater than 1.063 g/mL. These fractions are remarkably similar in hamsters and humans[19] and correspond to TG-rich lipoproteins (which include chylomicrons, very–low-density lipoproteins, and intermediate-density lipoproteins), LDL, and high-density lipoprotein (HDL), respectively.

The luminal area of aorta affected by lipid deposition was determined as follows: Aortas were rinsed in 60% isopropanol, immersed in oil red O (in 60% isopropanol) for 25 minutes, blotted dry, and rinsed with Na cacodylate buffer for 1 minute. Aortas were then opened longitudinally and mounted with the luminal surface facing upward on a glass slide with a cover slip and aqueous mounting medium. Each aorta was scanned and digitized using light microscopy at a magnification of 10× and a C. Imaging video digitizer (Compix, Mars, PA). Sixteen fields representing the entirety of the aorta were examined. The oil red O–stained area was quantified in square microns using the software program provided with the system.

Statistical differences between means were determined by Student's *t* test for paired groups and by one-way ANOVA for multiple groups, using Fisher's paired least-significant difference to establish significance at P less than .05. Coefficients of variation (CVs) were calculated with the following formula: standard deviation × 100/mean = CV (%).

RESULTS

At the start of the diet periods, there was no significant difference in body weights between males (107 ± 10 g) and females (110 ± 12 g). Food amounts were calculated for 1 week at the end of each 12-hour light cycle for male and female hamsters (n = 12 per group). Significantly more food was eaten by females (8.8 ± 0.9 [SD] g/d) than males (7.0 ± 1.2) throughout the diurnal cycle ($P < .0001$). Females and males similarly ate during both phases of the light cycle, with the percentage of food consumed during the dark period greater than the percentage consumed during the light period (females 55.1% ± 3.0% and males 60.1% ± 4.3% during the dark phase). During the 5-week period of study, females gained significantly more weight than males on both the chow and HiFat diets (Fig 1). Furthermore, whereas weight gain in females was markedly enhanced by the HiFat diet, there was no difference in weight gain in males on HiFat versus chow diet.

After only 4 days of the HiFat diet, serum TG levels were

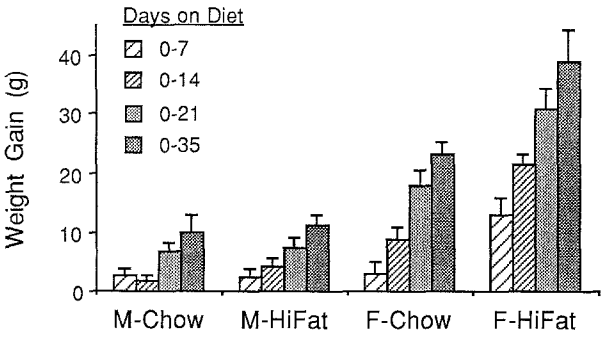

Fig 1. Change in body weight of F_1B hamsters during 5-week period on chow and HiFat diets. Mean ± SEM for 6 to 8 animals per group. At each period, weight change in female (F) animals was significantly greater at $P < .05$ (or less) than in male (M) animals on the same diet (with exception of values at 0 to 7 days for the F-Chow group). At each period, weight change in F-HiFat group was significantly greater than in F-Chow group.

significantly higher in freely feeding males than in female hamsters and remained markedly higher throughout a 5-week period of observation (Fig 2). Moreover, on the HiFat diet, serum TG levels in female hamsters were no different than levels in either male or female animals fed chow. Serum CH response to the HiFat diet paralleled the response of TGs and was significantly higher in male hamsters than in females as early as 4 days after the start of the diet. CH again remained higher in males than in females throughout this period of observation. However, in contrast to the lack of response of TGs in females, with HiFat there was a modest but significant increase in CH as compared with the chow diet. Although there was considerable variability in the response of individual animals in each diet group, in individual animals fed the HiFat diet the response tended to be similar when samples at different time points were compared. For example, in males fed HiFat, the CV calculated for the last two points at which lipid levels were measured (at 21 and 35 days, when values had seemingly reached a plateau) showed less variation when comparing the CV of the means of individual animals (17.9% ± 14.1% for TGs and 14.5% ± 9.4% for CH) with the CV of this group as a whole (44.1% for TGs and 33.1% for CH).

The distribution of CH in serum lipoproteins was determined after 3 weeks of HiFat and chow diets in a second group of freely feeding male and female hamsters (Table 1). (Total serum TG and CH levels were comparable to the values for animals shown in Fig 2.) In chow-fed animals, there were no significant differences between males and females in the distribution of CH in any lipoprotein fraction, and in both males and females most CH was in the HDL fraction. When HiFat was fed to males, there was a sizable increase in CH in all lipoprotein fractions, with the greatest percent increase in TG-rich lipoproteins as compared with the chow-fed group. When HiFat was fed to females, there was no increase of CH in TG-rich lipoproteins, a smaller but significant increase of LDL CH as compared with males, and a significant increase of HDL CH comparable to the increase of HDL CH in males.

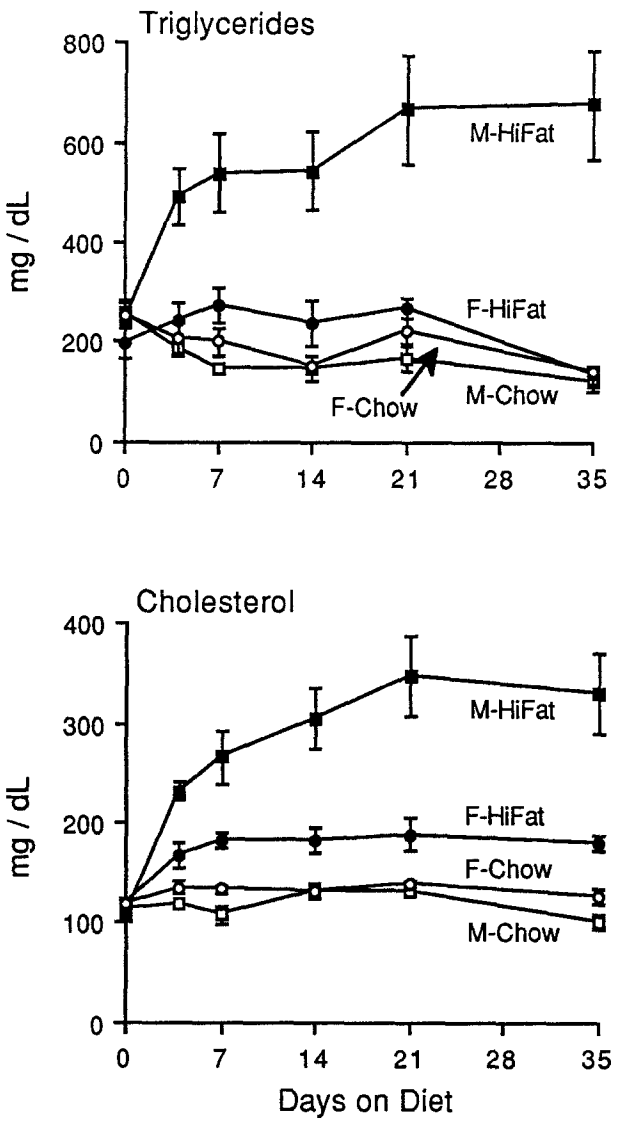

Fig 2. Changes in serum TG and CH of hamsters fed chow and HiFat diets. Mean ± SEM for the same groups shown in Fig 1. All TG and CH values were significantly greater at $P < .05$ (or less) in M-HiFat than in all other groups at each period. CH values were significantly greater at $P < .05$ (or less) in F-HiFat than in either M-Chow or F-Chow diet groups at each period.

Again, only in males fed the HiFat diet was there an increase in serum TGs, and greater than 90% of this increase was in the TG-rich lipoprotein fraction (data not shown).

Table 1. Distribution of CH (mg/dL) in Serum Lipoproteins After 3 Weeks on Diets

Group	d < 1.019 g/mL	d 1.019-1.063 g/mL	d > 1.063 g/mL
Chow diet			
Female	16.6 ± 2.1	34.3 ± 2.0	96.1 ± 5.0
Male	14.0 ± 4.4	34.9 ± 7.0	67.4 ± 3.0
HiFat diet			
Female	13.9 ± 1.8	54.5 ± 7.3†	123.8 ± 14.4‡
Male	87.4 ± 18.7*	128.9 ± 7.0*	134.6 ± 17.6‡

*$P < .05$ *v* all other groups.
†$P < .05$ *v* female and male chow-fed.
‡$P < .05$ *v* chow-fed of same gender.

The response of female hamsters to the HiFat diet was also determined after castration (Fig 3). Although a response was delayed, with a HiFat diet a marked increase in both serum TGs and CH occurred, which by 3 to 5 weeks was virtually identical in ovariectomized females to the changes shown in males (Fig 2). Compared with females fed HiFat that had not been subjected to surgery (Fig 1), castration did not affect weight gain, which averaged 36 ± 8 g in 5 weeks and was the same as in sham-castrated females (38 ± 13 g).

A separate group of animals that had been maintained on diets for 2 weeks were singly caged and fasted for 18 hours. With fasting, serum TG levels were markedly reduced in males on the HiFat diet to the values of the other groups (Table 2). In contrast, serum CH was not changed as compared with values shown in Fig 2 and was still appreciably higher in males than females.

As a result of the HiFat diet, male hamsters maintained on diets for 12 weeks had a striking increase in fat deposition in the aortas as compared with chow-fed animals

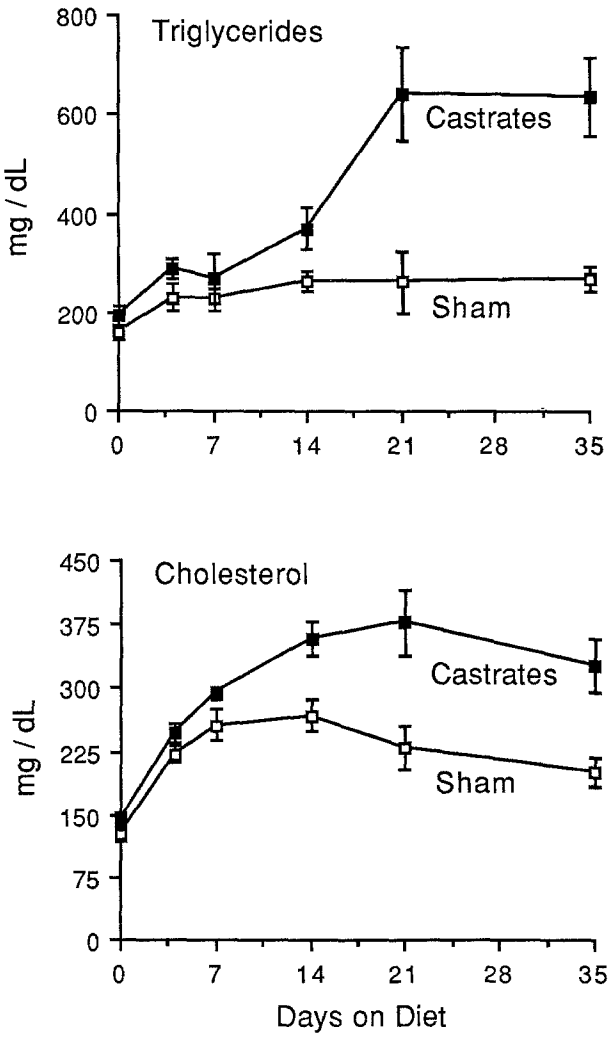

Fig 3. Serum TG and CH changes in response to a HiFat diet after ovariectomy. Mean ± SEM for 7 animals per group. All values at 2 weeks and thereafter were significantly different between groups at $P < .02$ (or less).

Table 2. Effect of Fasting on Serum Lipids (mg/dL)

Group	TG	CH
Chow diet		
Female	99 ± 25	120 ± 4
Male	46 ± 8	122 ± 3
HiFat diet		
Female	122 ± 29	189 ± 11†
Male	108 ± 16	271 ± 17*

*$P < .05$ *v* all other groups (by ANOVA).
†$P < .05$ *v* female and male chow-fed groups.

and female animals that were also fed the HiFat diet (Fig 4). The increased amount of lipid quantified by oil red O staining of the luminal surface of thoracic aorta in males corresponded to an increase in subintimal foam cells (by transmission electron microscopy) that were one to two cell layers in depth (micrographs not shown).

DISCUSSION

Our studies show that in at least one strain of Syrian hamsters, the F_1B hybrid, a diet with increased saturated fat and an amount of added CH that closely approximates the diet of Western populations[4] results in a marked increase in serum TG and CH levels in freely feeding male but not female animals and in changes consistent with early atherosclerosis in the aortas of male but not female animals. Serum lipid changes in males occurred early after starting this diet, were sustained for a period of weeks, and were notable for an increase in CH of approximately equal magnitude in all lipoprotein fractions, separated as TG-rich lipoproteins, LDL, and HDL. However, in freely feeding animals the greatest percentage increase in CH was by far in the TG-rich lipoprotein fraction (Table 1). In contrast to males, in females fed this saturated fat diet there was no increase in serum TGs and a much smaller increase in serum CH that was almost evenly divided between LDL and HDL fractions (Table 1).

The greater amount of TG-rich lipoproteins in male as compared with female hamsters is remarkably similar to lipid patterns in cross-sectional studies of human males and premenopausal females in the West[20] and similar to changes that occur in the postprandial state in human males and females.[21,22] Differences in serum TG and CH levels in male and female hamsters (Fig 2) were abolished when females were castrated (Fig 3), and this observation is again highly consistent with the changes that occur in the human female with either a natural or surgically produced menopause.[23,24] At this time, we do not have an explanation for the gender difference in TG response to this HiFat diet. Because serum TG levels were measured in freely feeding and not fasted animals, differences in TGs might reflect differences in lipase-mediated clearance of TG-rich lipoproteins that may be influenced by sex hormones.[25] The reduction of TG levels in males on the HiFat diet with a prolonged period of fasting (Table 2) is consistent with an impairment of TG clearance in this group, but is also consistent with a reduction in the input of TGs from the intestine and/or liver in newly synthesized lipoproteins.

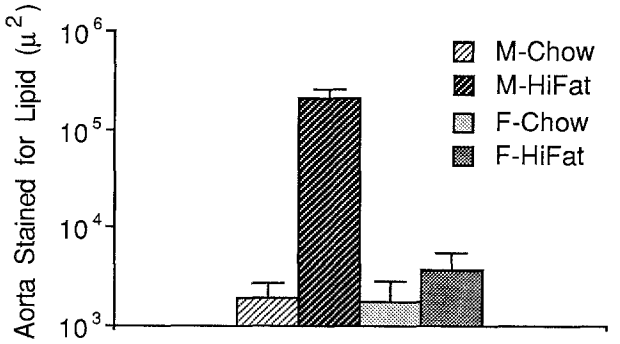

Fig 4. Extent of aortic lipid deposition in M and F hamsters after a diet period of 12 weeks. Values shown as scores on a log scale ± SEM for 10 animals per group. $P < .05$ (or less) for M-HiFat *v* all other groups.

We did not routinely fast the animals in this study, in order to preserve natural diurnal cycles and a constant environment for serial serum lipid determinations. Males and females ate at the same times throughout a 24-hour period, and females actually ate more than males and clearly gained more weight than males (Fig 1). It is thus unlikely that the higher concentrations of serum TG in freely feeding male hamsters can be attributed to a difference in eating, since we further found that there were relatively small intraindividual variations in TG levels in animals on the HiFat diet when lipids were compared at two periods of this study, suggesting that differences between males and females were due to differences in metabolism rather than to some difference in the manner that samples were obtained.

With fasting, gender differences in serum CH were maintained. Although we did not determine the distribution of CH in lipoproteins after fasting as we did in freely feeding animals, it can be anticipated from the known precursor relationship of TG-rich lipoproteins to LDL that most of the CH that was no longer in TG-rich lipoproteins with fasting was in LDL.

Morphologic changes consistent with the early lesions of atherosclerosis were found with regularity in the thoracic aortas of only male hamsters fed the HiFat diet. The extent of lesioned areas was estimated by lipid staining of the luminal surface of the aorta, and in male animals a significant increase in lipid staining (Fig 4) was observed that corresponded to an increase in foam cell accumulation by electron microscopy. No visible disruption of the luminal surface was evident (ie, fatty streak formation), and the increase in fat deposition was confined to subintimal macrophages. These changes correspond to the "type I" lesions of developing atherosclerosis as defined by Stary et al[15] and have previously been reported in this strain[16] and other hamsters[13] fed a similar diet.

Although there are a number of aspects of lipid and sex-hormone metabolism that need to be explored in these hamsters to explain the differences in response of males and females to this diet, there are parallels between these hamsters and humans that suggest this small animal may be highly appropriate as a model of human atherosclerosis. In particular, and unlike other kinds of animals that have been fed similar diets, freely feeding male (and castrated female) hamsters of the F_1B strain have a major increase in TG-rich

lipoproteins that closely corresponds to the higher levels of postprandial TGs that have been repeatedly found in subjects with established coronary heart disease,[26,27] and moreover appear to predict the development of coronary atherosclerosis.[28] However, it is notable that unlike many humans with coronary atherosclerosis, HDL CH concentrations in male hamsters with evolving atherosclerosis were not low, but with the HiFat diet were the same as for female hamsters and were significantly higher than for both male and female control groups fed chow (Table 1). A high saturated fat diet has been regularly found to increase HDL CH and LDL CH in laboratory animals, as well as humans.[29-31] However, hamster plasma has a low level of CH ester transfer protein activity,[32] and unlike humans with increased concentrations of TG that are ordinarily exchanged for CH ester in HDL,[33,34] higher concentrations of TG in the hamster do not result in a loss by exchange of CH ester from HDL.[32]

Finally, we do not know if the gender differences in response to this HiFat diet in the F_1B strain of hamsters can be expected in other genetic strains of hamsters. Substantial differences have been reported in plasma lipids[35] in different colonies of hamsters. However, in other strains of hamsters the focus of research has been primarily on the changes in LDL metabolism that are diet-related.[3-6] If, as for the F_1B hamster, other hamsters also ordinarily eat during both the dark and light cycles of a 24-hour period, then hamsters may always be in a postprandial state and the metabolism of TG-rich lipoproteins in these animals may be as germane to the development of atherosclerosis as the metabolism of LDL.

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