

Change in Rats' Serum Triglyceride Concentration with Graded Levels of Thyroxine and Exercise (39674)

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In 1964, Holloszy *et al.* (1) demonstrated that exercise had a significant effect on lowering serum triglyceride (TG) levels in middle-aged men. Subsequently, other investigators reported similar findings in exercised men (2-5) and rats (6-11). However, other investigators have also reported that exercise has no effect on (12, 13) or increases (14-16) the concentration of plasma TG. Thus, the literature regarding the effects of exercise upon serum triglyceride is confusing and often contradictory (5, 10).

In horses (17) and in rats (18-20), exercise is known to increase thyroid secretion rate. It has long been known that thyroxine plays a significant role in the regulation of lipid metabolism (21, 22). We have shown that the intact thyroid gland is necessary for the hypocholesterolemic effect of exercise (23, 24).

In view of the fact that high lipid concentration in serum is a risk factor associated with increased incidence of premature coronary heart disease (38-41), we investigated one possible means of lowering the serum triglyceride level. We examined the role of the thyroid gland on the hypotriglyceridemic response to physical exercise.

Materials and Methods. Experimental design. The study was designed as a 4×5 analysis of variance factorial experiment in which each of the 20 treatment combinations contained 12 male rats (Sprague-Dawley-Rolfsmeier) weighing 220 ± 20 g at the initiation of the experimental period.

Thyroid groups. Five different thyroid states were produced. Four groups of surgically thyroidectomized male rats were given daily replacement therapy of either saline or L-thyroxine (L-T₄): (i) no L-T₄ replacement (saline injection); (ii) 0.5 μ g of L-T₄/100 g body wt; (iii) 1.0 μ g of L-T₄/100 g body wt; and (iv) 3.5 μ g of L-T₄/100 g body wt. A

fifth group of rats with intact thyroids served as the controls. The L-T₄ dose level to produce the thyroid states was based on the studies of Kumaresan and Turner (25) on male rats of the same strain and commercial supplier as the strain used in our study. The 1.0 μ g of L-T₄/100 g body wt was considered a euthyroid dose, whereas the 0.5 and 3.5 μ g of L-T₄/100 g body wt were considered hypo- and hyperthyroid dosages, respectively.

Exercise groups. The five thyroid groups were further subdivided into four levels of physical activity: (a) nonexercised controls, (b) standing in 7.6 cm of water to check the possibility of water-induced stress, (c) moderate exercise, and (d) exhaustive exercise. Daily swimming was employed in groups c and d. The criterion for rats swimming until exhausted was allowing each rat to swim until it could no longer remain swimming above water. To decrease the swimming time and to stimulate more vigorous swimming, lead weights (4% of body weight) were attached to the tail, and, to reduce the buoyancy effect of trapped air under the fur, a wetting agent was added to the water. Moderate exercise was arbitrarily established as one-half the mean weekly swimming time of the respective exhaustively exercised groups (group d). The animals swam individually in 20-gallon plastic tanks 6 days a week for 10 weeks. Since McArdle and Montoye (26) demonstrated that pretraining periods significantly improved the reproducibility of the swimming time to exhaustion, a 1-week pretraining period was enforced by increasing the weight load 0, 2, and 4% of the body weight every second day. Water temperature was maintained at $37 \pm 2^\circ$. The rats were weighed every other day. The daily feed consumption of each rat was recorded. Drinking water and feed

(Wayne Lab-Blox) were provided *ad libitum*.

Serum analysis. At the end of the experimental period, the rats were fasted for 12–16 hr, bled via the thoracic aorta, and then killed. At this time, a postmortem check for remaining thyroid tissue was performed in the surgically thyroidectomized animals. The sera was analyzed for TG content (27).

Results and discussion. Analysis of variance (28) indicates that the main effect of thyroid status (A), the main effect of physical activity (B), and the AB interaction had a highly significant influence ($P < 0.0005$) on the serum TG level (Table I). Analysis of covariance indicates that the varying feed intake (Fig. 1) of the 20 groups was not an important factor in influencing the serum TG concentrations when the animals were fed a basal diet. This suggests that the serum TG levels represent primarily endogenous TG. The unadjusted means were used when determining the effects of the thyroid status and physical exercise on serum TG levels.

Effect of thyroxine. When compared to the control animals with intact thyroids, serum TGs of the 0, 0.5, 1.0, and 3.5 μg of L-T₄-treated groups were found to be significantly lower ($P < 0.0001$). This difference in serum TG levels may be related, in part, to body weight. Figure 2 shows the final body weights of the various treatment groups. When compared to the control rats, irrespective of the level of physical activity,

the 0 μg of L-T₄-treated group (athyroid group) had the lowest body weights and, generally, the lowest serum TG concentrations, as compared to the other groups. A similar trend is seen in the 0.5, 1.0, and 3.5 μg of L-T₄-treated groups, i.e., their body weights were lower than those of the control rats with intact thyroids, and their serum TG levels were also lower than the levels of the control groups.

Effect of exercise. The serum TG levels were lower (main effect or overall mean) in the moderately exercised groups ($0.02 < P < 0.05$) and exhaustively exercised group ($P < 0.001$), when compared to the control animals. This is in agreement with previous studies (6–11, 20). The results of this investigation indicate that (i) exercise is effective in lowering serum TG, and (ii) this hypotriglyceridemic response is directly related to the increasing severity of exercise. It appears, that, while this form of exercise has some hypocholesterolemic effect in rats (24), the hypotriglyceridemic response is more pronounced.

The mechanism for this change is not clearly understood. In our previous study (20), we demonstrated that the same exercise program used in this study resulted in an effective increase in thyroid secretion rate (TSR) in both young and mature rats. It is possible that the cause of the decreased plasma TG during exercise may be due to a decreased TG efflux into the plasma. Since

TABLE I. INFLUENCE OF DIFFERENT LEVELS OF PHYSICAL ACTIVITY AND THYROXINE ON SERUM TRIGLYCERIDE CONCENTRATION (mg/100 ml \pm SEM)

Thyroid status ^b (μg of T ₄ /day)	Physical activity ^a				Overall mean (A)
	No exercise	Standing	Moderate exercise	Exhaustive exercise	
Control	88.9 \pm 5.2 ^c	69.5 \pm 4.2 ^d	59.3 \pm 3.3 ^d	55.7 \pm 3.4 ^e	68.4 \pm 4.0
3.5	47.5 \pm 2.8 ^e	48.8 \pm 4.7	49.1 \pm 2.9	42.1 \pm 2.6	46.9 \pm 3.3 ^e
1.0	57.8 \pm 3.5 ^e	56.9 \pm 3.5	51.5 \pm 3.2	37.9 \pm 2.3 ^f	51.0 \pm 3.1 ^e
0.5	62.9 \pm 3.8 ^e	48.5 \pm 3.0	50.3 \pm 3.0	32.9 \pm 2.0 ^d	48.7 \pm 2.9 ^e
0	43.7 \pm 2.9 ^e	36.3 \pm 2.3	50.7 \pm 3.1	33.9 \pm 2.1	41.2 \pm 2.7 ^e
Overall mean (B)	60.2 \pm 3.6	58.0 \pm 3.5	52.2 \pm 3.1 ^g	40.5 \pm 2.5 ^e	

^a One SD (0.05) for physical activity (B = main effect) = 6.4 mg/100 ml.

^b One SD (0.05) for thyroid status (A = main effect) = 7.2 mg/100 ml.

^c One SD (0.05) for AB (interaction) in 14.3 mg/100 ml.

^d $P < 0.01$, when compared to control group.

^e $P < 0.001$, when compared to control group.

^f $0.05 < P < 0.1$, when compared to control group.

^g $P < 0.05$, when compared to control group.

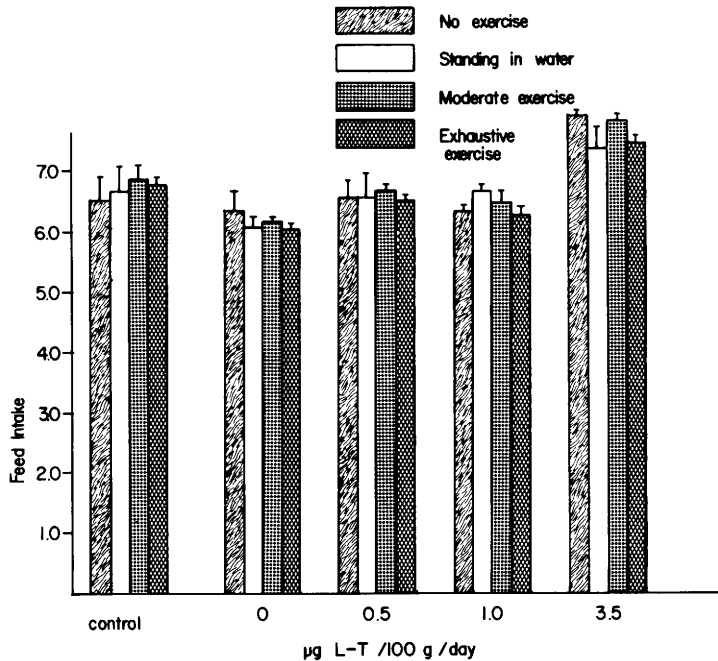


FIG. 1. Feed intake (g/100 g body weight/day) of the four groups of exercised rats (no exercise, standing in water, moderate exercise, and exhaustive exercise) that have either intact thyroid (control) or no thyroid (0 μg of L-T/100 g/day) or no thyroid with replacement therapy (0.5, 1.0, or 3.5 μg of L-T/100 g/day). L-T = L-thyroxine, Na salt. Values are expressed as mean ± SEM.

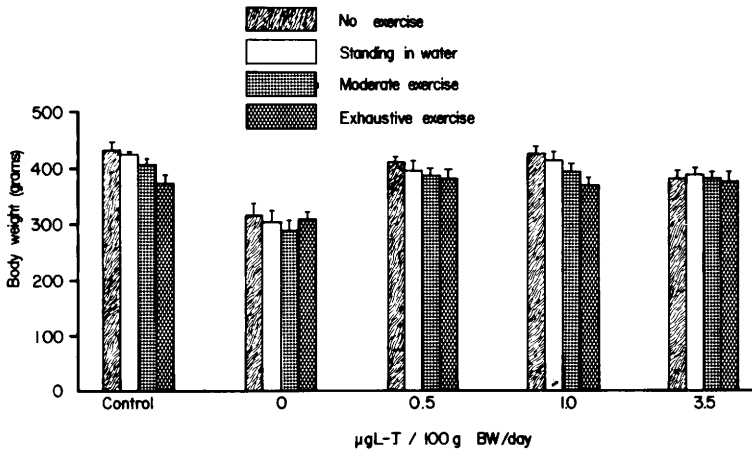


FIG. 2. Body weight (grams) of the four groups of exercised rats that have either thyroid, no thyroid, or no thyroid with daily replacement therapy of L-thyroxine, Na salt. Values are expressed as mean ± SEM.

a large portion of the endogenous plasma TG is derived from the liver, a decreased efflux of TG to plasma could be caused by a decreased secretion of endogenous hepatic TG into the plasma. This might occur as a result of decreased hepatic uptake of plasma FFA for TG synthesis (8, 29). While the mobilization of FFA from adipose tissue is

actually increased (30, 31), plasma FFA uptake by the muscles is also increased (8, 32, 33). The increased plasma FFA uptake by the muscles may be the result of (i) FFA as the preferential fuel for muscles during the elevated metabolic demand of exercise or (ii) a change in the distribution of blood flow during exercise. It is known that blood

flow through the working muscles is increased (32-34), whereas hepatic blood flow is considerably reduced during heavy exercise (35). This suggests that the uptake of plasma FFA by the liver may be decreased during exercise, which may result in a decreased formation of TG in the liver.

Another possible mechanism by which hypotriglyceridemia might occur as a result of increased physical activity may be due to the increased influx of TG from the plasma into tissues. Nikkilä *et al.* (36) reported that lipoprotein lipase activity was increased in rats forced to exercise. The increased lipase activity increased the FFA available to the working muscles for fuel. The increased lipoprotein lipase activity may be the result of increased TSR due to exercise. Porte *et al.* (37) reported that lipoprotein lipase activity is increased after thyroxine therapy. In our previous study on rats, we showed that the intact thyroid gland is necessary for exercise to induce hypocholesterolemia (24). This present study also suggests that the thyroid gland, in some manner, participates in the hypotriglyceridemic effect of elevated physical activity.

Summary. Male thyroidectomized rats with varying levels of daily L-thyroxine injection were subjected to different amounts of physical activity to determine the influence of both factors on serum TG concentration. The study indicated that exercise is effective in lowering serum TG and that this hypotriglyceridemic response is directly related to the increasing severity of exercise. The control animals with intact thyroids had higher TG levels as compared to the thyroidectomized rats with differing replacement levels of L-T₄ irrespective of the degree of physical activity. The differing feed intake in the various groups could not account for this hypotriglyceridemic effect. The lower body weight of the thyroidectomized animals, as compared to the control rats with intact thyroid glands, may be related, in part, to the lower TG concentration. The study suggests that the thyroid gland, in some manner, plays an important role in the hypotriglyceridemic effect of exercise.

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