

The Association between Popular Diets and Serum Testosterone among Men in the United States



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Abbreviations and Acronyms

BMI = body mass index
NHANES = National Health and Nutrition Examination Survey
SHBG = sex hormone binding globulin
T = testosterone
TD = T deficiency

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Purpose: We examined the relationship of the serum testosterone level to low fat, Mediterranean and low carbohydrate diets in a large, nationally representative patient sample.

Materials and Methods: We queried the NHANES (National Health and Nutrition Examination Survey) from 1999 to 2000, 2003 to 2004 and 2011 to 2012. Men 18 to 80 years old who completed the 2-day dietary history and underwent serum testosterone testing were included in analysis. Diets were categorized as low fat, Mediterranean, low carbohydrate or nonrestrictive. Multivariable modeling was used to determine the relationship between diet and serum testosterone.

Results: Of the 3,128 men who met study inclusion criteria 457 (14.6%) and 764 (24.4%) met the criteria for a low fat and a Mediterranean diet, respectively. Only 2 men (less than 0.1%) met the criteria for a low carbohydrate diet, which was removed from further analysis. Mean \pm SD serum testosterone was 435.5 ± 6.7 ng/dl. Mean testosterone was lower among men with a low fat diet (410.8 ± 8.1 vs 443.5 ± 7.3 , $p=0.005$) and a Mediterranean diet (412.9 ± 9.1 vs 443.5 ± 7.3 , $p=0.002$). Multivariable analysis controlling for age, body mass index, activity level, diabetes, comorbidities and prostate cancer showed that men with a nonrestrictive diet had higher serum testosterone than those adhering to a low fat diet ($\beta -57.2$, 95% CI -105.6 to -8.8 , $p < 0.05$).

Conclusions: Men adhering to low fat diets had lower serum testosterone levels even when controlling for comorbidities, age, body mass index and activity levels. As differences in serum testosterone between the diets were modest, the avoidance of fat restrictive diets should be weighed against the potential benefits on an individual basis.

Key Words: testosterone; diet, fat-restricted; dietary carbohydrates; diet, Mediterranean; deficiency diseases

TESTOSTERONE deficiency is highly prevalent in the United States. Multiple longitudinal studies have estimated that anywhere from 20% to 50% of men have low serum T and approximately 500,000 are newly diagnosed with TD annually.¹⁻³ TD may cause bothersome symptoms such as

decreased energy, libido, erectile function, and changes in mood and cognition.⁴ TD can cause physiological alterations leading to increased visceral fat, decreased lean body mass and reduced bone mineral density.^{4,5} Furthermore, there is evidence that TD is associated with other chronic

disease states such as diabetes mellitus and cardiovascular disease.⁴

TD treatment often begins with pharmacological intervention, although increasing evidence supports a multifaceted treatment approach incorporating lifestyle modifications.⁶ Numerous studies have demonstrated that exercise and weight loss can improve serum T in men and yet the effects of diet are not well understood.^{7,8} Specifically, sparse literature has explored the effects of individual macronutrients on serum T in males.⁸ While there is some evidence that weight loss secondary to dietary changes may increase serum T, other studies have shown that similar diets in otherwise healthy men may actually decrease T.^{9–11} As T is a steroid hormone derived from cholesterol, changes in fat intake could alter T homeostasis.

It is estimated that in 2018 nearly 45 million Americans trialed some type of new diet.¹² Given the absence of data describing the effects of specific popular diets on serum T, we sought to examine the relationship of the AHA (American Heart Association) low fat, Mediterranean and low carbohydrate diets with the serum T level in a large, nationally representative patient sample.^{13–16}

MATERIALS AND METHODS

Data Source and Study Population

The NHANES is a cross-sectional data set aggregated by the CDC (Centers for Disease Control and Prevention) designed to determine the general health of the American populace.¹⁷ All study subjects submitted a written consent, which was approved by the NCHS (National Center for Health Statistics) Ethics Review Board. The Northwestern University Feinberg School of Medicine Institutional Review Board deemed this study exempt from review.

Data were limited to the 1999 to 2000, 2003 to 2004 and 2011 to 2012 data cycles since only they included T values. The study population was further limited to men 18 to 80 years old who completed the full 2-day dietary history. We selected the low fat, Mediterranean and low carbohydrate diets based on the DIRECT (Dietary Intervention Randomized Controlled Trial) group criteria.¹³ These diets were chosen because popularity, safety and efficacy are well established.^{12–16}

Dietary Intake Assessment

The dietary recall validity, methodology and clinical applicability have been described previously.^{17–19} We

assessed the dietary data integrity of each participant using 2 metrics. 1) The NHANES includes an internal quality control for dietary recall status and only subjects who were considered reliable were included in analysis. 2) Only subjects who answered “usual” to the question, “Was the amount of food that you ate yesterday much more than usual, usual or much less than usual?” were included.

The patients were stratified into diet type based on the average composition of macronutrients consumed during a 2-day period. Analyzed diets included the AHA low fat diet, low carbohydrate diet and the Mediterranean diet based on previously established criteria (table 1).^{13–16} Since the diets were not mutually exclusive, all comparisons were made between men in a particular diet group vs men not in any diet group (ie nonrestrictive).

Covariables and Primary Outcome

All questionnaire data, including medical diagnoses and demographic information, were self-reported by the subjects. In addition to basic demographic information such as age, income, race and education level, we analyzed the covariables comorbidities, activity level, substance use, BMI, prostate cancer history, and levels of SHBG and albumin. A previously established NHANES specific comorbidity index was used to assess subject comorbid conditions.²⁰ The conditions included in this index are 1) arthritis, 2) congestive heart failure, 3) asthma, 4) myocardial infarction, 5) cancer and 6) stroke. Given the integral role of metabolic syndrome and diabetes in TD, they were considered independent variables.

Activity level was determined by the participant response to certain questions, including 1) “Over the past 30 days, did you do any vigorous activities for at least 10 minutes that caused heavy sweating or large increases in breathing or heart rate?” 2) “Over the past 30 days, did you do moderate activities for at least 10 minutes that cause only light sweating or a slight to moderate increase in breathing or heart rate?” An affirmative response to question 1 classified participant activity as vigorous, a negative response to question 1 followed by an affirmative to question 2 classified participant activity as moderate and a negative response to questions 1 and 2 classified participant activity as less than moderate.

Our primary outcome was the effect of diet on total serum T. The secondary outcome was the presence of serum T less than 300 ng/dl, which is the accepted TD cutoff according to the AUA (American Urological Association) guideline on T deficiency.⁶ T values in the NHANES were measured using a validated, isotope dilution, liquid chromatography tandem mass spectrometry method.²¹ Serum T was measured at a single time point in the morning or the

Table 1. Popular diet macronutrient parameters^{1–4}

	Diet		
	Low Fat	Low Carbohydrate	Mediterranean
Calories (kcal)	1,800 or Less	Not applicable	1,800 or Less
Carbohydrates (gm)	Not applicable	20 or Less	Not applicable
Fat (% total calories)	30 or Less	Not applicable	40
Saturated fat (% total calories)	10 or Less		Not applicable
Cholesterol (mg)	Less than 300		Not applicable

afternoon. We performed sensitivity analysis to control for the timing of the laboratory draw and fasting status, which did not alter the results of the analysis.

Statistical Analysis

We combined 2-year data sets from 3 periods, including 1999 to 2000, 2003 to 2004 and 2011 to 2012, using respondent sequence numbers. To account for the complex design of the NHANES we used the strata, cluster and sample weights directed by the NCHS in the mentioned analyses.²²

Demographic characteristics were compared in men adhering to a low fat vs a nonrestrictive diet and a Mediterranean vs a nonrestrictive diet using the chi-square test and the t-test as applicable. Univariable linear regression was performed to determine the association between baseline characteristics and serum T. Only variables with a significant association were included in the subsequent multivariable model. We performed multivariable linear regression to explore serum T as a continuous variable and logistic regression using serum T less than 300 ng/dl as a dichotomous variable. Identified confounders included on multivariable analysis were patient age, BMI, income, diabetes status, comorbidity index, race, activity level, SHBG, albumin and diet. Adjusted regression coefficients (β), and the OR and 95% CI were calculated to explore the association between the identified confounders and outcome variables. Two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SAS®, version 9.4.

RESULTS

Diet

Of the 3,128 men who met study inclusion criteria 973 (31.1%) did and 2,156 (68.9%) did not meet the criteria for a restrictive diet. Of the men adhering to a restrictive diet 764 (78.5%), 2 (less than 1.0%) and 457 (47.0%) met criteria for a Mediterranean, a low carbohydrate and a low fat diet, respectively. Given the limited number of men in the low carbohydrate group, no additional analysis was performed.

Supplementary table 1 (<https://www.jurology.com>) lists demographic characteristics of the men in each dietary category. Men adhering to a Mediterranean and those on a low fat diet were on average older than men with a nonrestrictive diet (50 and 49 years, respectively, vs 43, each $p < 0.001$). Compared to men adhering to a Mediterranean diet and men on a low fat diet, those on a nonrestrictive diet were less likely to have diabetes (10.0% vs 19.4% and 19.0%, each $p < 0.001$), more likely to engage frequently in vigorous physical activity (28.6% vs 18.7% and 18.7%, $p < 0.001$ and $p = 0.001$, respectively) and less likely to have 1 or more comorbidities (39.5% vs 47.5% and 46.4%, each $p = 0.01$).

Serum Hormone Levels

Average serum T in the entire cohort was 435.5 ± 6.72 ng/dl. Of the men 838 (26.8%) had serum T less than 300 ng/dl. Across the entire cohort SHBG was 37.01 nmol/l and albumin was 44.64 gm/l. Average

SHBG was 36.68 ± 1.13 vs 40.20 ± 2.35 ($p = 0.144$) and 40.82 ± 3.77 nmol/l ($p = 0.269$) in men who conformed to a nonrestrictive diet compared to men on a Mediterranean and a low fat diet, respectively. Likewise, serum albumin was 44.33 ± 0.12 vs 43.71 ± 0.15 and 40.82 ± 3.77 gm/l ($p < 0.001$ and $p = 0.004$) in men who consumed a nonrestrictive diet compared to a Mediterranean and a low fat diet, respectively.

Laboratory draw time, which was analyzed separately, had no significant effect on any covariate on multivariable analysis and it did not predict diurnal variation in this specific data set, as previously demonstrated.²³

Diet and Serum Testosterone Relationship

On univariable analysis men who adhered to a low fat diet had lower serum T than men on a nonrestrictive diet (410.81 ± 11.34 vs 443.47 ± 7.31 ng/dl, $p = 0.002$, supplementary table 1, <https://www.jurology.com>). Likewise men who adhered to a Mediterranean diet had lower serum T than men on a nonrestrictive diet (412.90 ± 9.19 vs 443.47 ± 7.31 ng/dl, $p = 0.005$). On multivariable analysis men adhering to a low fat diet had lower serum T than men on a nonrestrictive diet ($\beta -57.22$, 95% CI -105.60 to -8.83 , $p = 0.02$). Similarly men on a Mediterranean diet had lower serum T than men on a nonrestrictive diet, although this did not reach statistical significance ($\beta -26.15$, 95% CI -61.92 – 9.62 , $p = 0.15$, table 2).

On multivariable analysis there was no significant difference in the proportion of men with serum T less than 300 ng/dl between the 2 groups (OR 2.30, 95% CI 0.73–7.30, $p = 0.15$, supplementary table 2, <https://www.jurology.com>). Likewise of the men who adhered to a Mediterranean diet there was no significant difference in the proportion of those with serum T less than 300 ng/dl in the 2 groups (OR 0.90, 95% CI 0.29–2.76, $p = 0.85$).

DISCUSSION

With the recent popularity of restrictive diets in the United States it is important to examine potential benefits and unintended consequences on personal health. While dieting for weight loss will clearly help optimize cardiovascular health with corresponding reductions in lipid profiles, the effect of diet on T is not well established.¹³ An early prospective trial demonstrated that low fat diets (less than 25% caloric consumption) had no effect on the T level during a 6-week period.⁹ A similar study by Rosenthal et al demonstrated that even greater reductions in fat intake (less than 10% caloric consumption) combined with the initiation of an exercise program had no significant effect on T.²⁴ However, in each small cohort patients at risk for cardiovascular disease were overrepresented and there was a heterogeneous distribution of body mass. A more recent study in

Table 2. Multivariable linear regression of diet and serum testosterone association

	β (95% CI)	p Value
Age	-4.67 (-6.83 - -2.50)	<0.01
BMI (kg/m ²):		
Normal (less than 25)	Referent	—
Overweight (25 to less than 30)	-40.87 (-77.96 - -3.78)	0.03
Obesity (30 or greater)	-18.54 (-169.86-132.78)	0.81
Income (\$):		
Less than 20,000	Referent	—
20,000 or Greater	5.39 (-34.16-44.94)	0.79
Diabetes	-6.04 (-81.61-69.53)	0.87
Comorbidity index:		
0	Referent	—
1	-72.69 (-157.56-12.19)	0.09
2	-75.82 (-195.28-43.64)	0.21
3	-184.26 (-326.91 - -41.61)	0.01
Greater than 4	-117.71 (-284.93-49.51)	0.16
Race:		
Mexican American (ref)	Referent	—
Other Hispanic	31.23 (-57.89-120.34)	0.48
NonHispanic White	30.37 (-57.83-118.57)	0.49
NonHispanic Black	149.99 (47.94-252.05)	<0.01
Other	33.93 (-43.03-110.88)	0.38
Activity:		
Vigorous	Referent	—
Moderate	93.90 (-44.41-232.21)	0.18
Less than moderate	-12.38 (-63.69-38.93)	0.63
SHBG (nmol/l)	4.76 (3.120-6.40)	<0.01
Albumin (gm/l)	8.33 (-10.96-27.62)	0.39
Diet:		
None	Referent	—
Mediterranean	-26.15 (-61.92-9.62)	0.15
Low fat	-57.22 (-105.60 - -8.83)	0.02

cohorts of healthy subjects with an average BMI of 27.8 kg/m² revealed that fat restricted diets (less than 15% caloric consumption) decreased serum T as much as 12%.²⁵ The discrepancies among these studies were likely due to the heterogeneity of the analyzed populations and variability in the restricted diets in the study, which made drawing population based conclusions challenging.

To our knowledge we present the largest analysis of the association between macronutrients and serum T using population based data. When controlling for BMI, activity level and comorbidities, we found that men who adhered to a fat restrictive diet had lower serum T than men on a nonrestrictive diet. However, we found no significant difference in the proportion of men with T less than 300 ng/dl across the diets. Thus, the clinical significance of small differences in serum T across diets is unclear.

If fat restrictive diets are used by overweight patients to achieve weight loss and improve comorbidity, these benefits likely outweigh the 30 ng/dl decrease in serum T. Indeed, numerous studies have shown an increase in serum T after weight loss in the overweight and obese patient populations.²⁶⁻²⁸ The increase in serum T after significant weight loss ranged from 182 to 240 ng/dl, a benefit which clearly outweighs the potentially detrimental effects of fat restriction.^{27,28} Even when considering more modest

estimates of improvement in serum T Moran et al found that restrictive diets associated with weight loss led to a 58 ng/dl increase in serum T regardless of the macronutrient composition.¹¹ That is, the benefits of weight loss seem to overwhelm the detrimental effects of fat restriction. Furthermore, weight loss can modulate obesity related conditions such as insulin resistance and obstructive sleep apnea, which can each decrease circulating T levels.²⁹

Alternatively in nonobese men the decrease in serum T associated with fat restrictive diets may be a reasonable target for a multifaceted approach to increasing serum T. It was hypothesized that extreme calorie or fat restriction in nonobese healthy men leads to significant decreases in serum T due in part to a lack of adequate precursors for steroidogenesis.^{8,30} The current study supports this hypothesis. Thus, we suggest that avoiding fat restriction should be considered when counseling nonobese and otherwise healthy men who present with hypogonadism or low normal T, or with general inquiry regarding lifestyle modification to improve endogenous T levels.

The strengths of the current study include the large sample size and the population based nature of the subjects. Furthermore, while to our knowledge other studies have focused exclusively on healthy, obese or comorbid patients in specific settings, the current patient population represents a real world, heterogeneous sample which may be more clinically applicable.

These data must be viewed within the limitations of our study design. 1) The NHANES is a cross-sectional data set which cannot account for potential longitudinal changes in diet, serum T, weight loss and other comorbidities. 2) Dietary intake was self-reported and, therefore, subject to recall bias. 3) Serum T was measured at only 1 time point but AUA guidelines recommend 2 levels due to intra-individual and diurnal serum T variations. 4) While multivariable analysis was done to account for important covariates, there may have been confounders even in these covariates. For example, activity level was included in analysis according to the basic categories captured by the NHANES questionnaire. However, the definition of vigorous was less strict than typically considered in other studies and, therefore, persistent confounding might exist in this category. Furthermore, unidentified or unmeasured confounders such as recent acute illness or receipt of T therapy could also have influenced our data. 5) The diets were calculated using metrics which have been well described previously.¹³⁻¹⁶ However, subject actual adherence to each diet as well as other survey based data was assumed based on subject recall and so subject to recall bias.¹³⁻¹⁶ 6) Finally, due to the progressive decrease in carbohydrate restriction of typical ketogenic diets, these dietary criteria only

captured men in the initial ketogenic phase of those diets. Thus, men in later, less restrictive phases of a ketogenic diet were not captured in the analysis.

Given these limitations, future prospective research is required to corroborate these findings and elucidate the mechanisms by which restrictive dieting may affect serum T. However, the challenges of designing, accruing and maintaining a dietary trial make this task daunting, given the high attrition rate. Furthermore, dietary trials are also population specific, making it difficult to arrive at generalizable conclusions. While a prospective trial would be ideal to delineate how diet affects T,

inherent challenges make this unfeasible. Therefore, our data represent a valuable (but not perfect) alternative answer to this important question.

CONCLUSIONS

In a nationally representative sample men who adhered to a low fat diet had lower serum T even when controlling for comorbidities, age, BMI and activity levels. As differences in serum T among the diets were modest, the avoidance of fat restrictive diets should be weighed against the potential benefits on an individual patient basis.

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EDITORIAL COMMENTS



It is established that obesity and metabolic syndrome correlate with T levels.¹ Men with these conditions would (theoretically) be the same men on weight loss diets. These authors found that T levels were lower in men on low fat diets compared with those on a nonrestrictive diet. They hypothesized that was due to the lack of T steroidogenesis precursors, which makes me wonder whether other hormone levels would also be altered. While low fat diets may be efficacious for weight loss, these data show that they may actually lower T, potentially trading one problem for another.

Structured diet and exercise programs have been shown to result in increased T levels.² While these authors accounted for physical activity to a limited degree (“vigorous activities for 10 minutes,” “over the past 30 days,” “that caused” (heavy/moderate/slight) “increases in breathing or heart rate”), this is less aerobic activity than was generally used in other

studies of at this topic (30 to 60 minutes 3 times per week). Additionally, data comparing the effect of caloric restriction vs aerobic exercise on T levels showed that aerobic exercise had a more substantial role on increasing T.² The lack of a more robust exercise measurement in this study makes me wonder whether this would have impacted the findings.

Regardless, these data suggest that moderation is key even in dieting. A comprehensive lifestyle approach (balanced diet, cardiac exercise, sleep optimization and stress reduction) may be best for our patients. This would optimize weight loss, maintain T and include the global health benefits of aerobic exercise.

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In 2018 approximately 45 million Americans trialed a new diet program.¹ While restrictive diets frequently yield many positive health outcomes, recent evidence indicates that low fat diets may reduce serum T levels. Fantus et al performed a heterogeneous, population based study in 3,128 men using data from the NHANES database and report a mean decrease in serum T levels of 33 ng/dl in men who followed low fat diets compared with a nonrestrictive diet.

Although statistically significant, the clinical significance of the measured 33 ng/dl decrease in T levels secondary to a low fat diet remains controversial, particularly in obese males. Pellitero et al reported an approximately 300 ng/dl increase in total T levels in 33 men following bariatric surgery.² This supports the conclusion that significant weight loss in obese males is more beneficial for improving serum T levels overall than the smaller, counter-

acting decrease in T which may result from a low fat diet. However, in nonobese, otherwise healthy men with hypogonadism increasing dietary fat consumption may prevent a decline in T and function as an adjunct in a multifaceted approach to maintain or increase serum T in this population, which includes a healthy diet and exercise.

The incorporation of restrictive diets, particularly low fat diets, may decrease serum T levels. This should be used on an individual basis in men with hypogonadism as the benefits may greatly exceed the potential decline in T which may result from such diets.

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REPLY BY AUTHORS



Exercise is a critical component of many weight loss regimens and it often accompanies restrictive diets, thereby potentially confounding the relationship between diet and T in any study. Indeed, Kumagai et al found that aerobic exercise positively correlated with the T levels, even more so than caloric restriction (reference 2 in comment). However, these results were restricted to a population of obese men and uncontrolled with respect to BMI, which may not translate to the nonobese population.

In this study we controlled for the potential effect of exercise on serum T and yet we acknowledge that the characterization of physical activity was not

traditional. Even with this less stringent characterization of vigorous physical activity, controlling for exercise should have minimized its effect as a potential confounder and shed light on the relationship between diet and T.

We hope that these data will help physicians better understand the complex relationships among diet, T and overall health. Ultimately restrictive diets are just one of the many lifestyle modifications which can affect serum T. These considerations should be weighed on an individual basis when counseling patients regarding serum T and overall health (reference 6 in article).