REVIEW

The Effects of Different Types of Diets on Steroid Hormone Concentrations

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Summary

The great popularity of various diets in recent years has led us to reflect on their suitability for our health. The aim of this communication is to review current knowledge on the influence of the most well-known diets on the concentrations of the main steroids and to consider possible mechanisms. The influence of diet on hormone concentrations is expected, but the literature data on this topic are inconsistent and yield conflicting results. The main problem in evaluating these influences is the change in weight that a change in diet induces. This effect needs to be filtered out in order to discover interesting associations between diet and steroid hormones. This is illustrated by the example of the effects of ketogenic diets on testosterone levels in men, where the direct effect of the diet is to reduce testosterone levels, but a number of papers have described increases that are due to diet-related weight loss and the modification of obesity-induced changes. A second major driver is the change in circadian rhythm, and it is necessary to assess hormonal changes induced by changing the time of day of the diet. Such shifts within the circadian rhythm rather than due to a particular type of diet itself are documented by changes in the circadian rhythm of cortisol.

Keywords

Testosterone • Estradiol • Cortisol - Ketogenic diet • Vegetarian diet • Intermittent fasting

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Introduction

The modern era is characterized by an increase in obesity and at the same time by the popularity of various "miracle" diets, in which the obese seek a solution to their extra pounds. Another strong driver of dietary changes and alternative diets are fashionable trends for a "healthy" lifestyle or various e.g. ecological tendencies. The influences of different religions on diet also continue to be strong. A wide range of diets can be found in the literature, and even more can be found on the internet. The awareness of diets among the general population is accompanied by a number of different myths and unrealistic expectations, both of which are difficult to explain and dispel. However, it is important to recognize that the relationship to a diet, as well as the motivation for choosing it, influences adherence and belief in its healthfulness and benefits. There is an immeasurable range of motivations for dietary change; these are not the subject of this communication, nor is assessing the suitability of a chosen diet for a given person. Rather, the purpose of this communication is to review the current knowledge of the effects of the most well-known diets on the concentrations of major steroids and to consider possible mechanisms.

Although the effects of diets on hormone concentrations are undisputed, the literature data on this topic is rather inconsistent and yields conflicting results. One major challenge in the approach to assessing results is the need to account for whether one is comparing differences between groups following different diets or

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comparing the same group before and after a change in diet over a relatively short period of adherence. Logically, these changes may not be the same for a given diet. An additional challenge, however, is the change in weight that the change in diet induces. Most hormonal changes are induced by the changes in weight, not by the type of diet itself. This effect needs to be filtered out, and only then can interesting connections between diet and steroid hormones be found. Hormonal changes induced by changes in the time of day of dieting should be evaluated with caution, as such changes are more likely to be due to shifts in circadian rhythm rather than the effects of a particular type of diet. These crucial factors will be discussed below.

What is a diet?

The term diet comes from the Greek word: diaita, Δίαιτα, which means lifestyle. However, the term is generally understood in the sense of a defined intake of food and fluid in order to achieve a specific goal.

Different diets

The Western diet

The term "Western" diet is used to refer to a way of eating characterized by a diet rich in red and processed meats, dairy products, refined grains, processed and artificial sweets, salt, and a minimal intake of fruits, vegetables, fish, and whole grains. I put the term "Western" for this type of diet rather in quotation marks, as it is not geographically bound, and industrially processed or global would be more appropriate. Because of its largely processed nature, the Western diet is increasingly cheaper and relatively easy to access due to industrialization and globalization. There is a growing body of evidence documenting the negative impacts of this type of diet on health [1], with these impacts most commonly associated with over-processing.

Mediterranean diet

The Mediterranean diet consists of fish, monounsaturated fats from olive oil, whole grains, vegetables, fruits, legumes and nuts. This diet has recently gained increasing popularity outside the region due to the growing evidence of related health benefits. Studies have documented reduced risks of mortality, cardiovascular disease, cancer incidence, neurodegenerative diseases and diabetes [2]. Thus, the Mediterranean diet has many benefits and there are no known health risks.

Paleolithic diet

The Paleolithic diet represents a return to the diet of our ancestors, namely hunters and gatherers before the agricultural revolution of modern times. The diet consists of lean meats, plant foods, fruits, vegetables, nuts and limited consumption of dairy products, cereals, sugar and salt. Health benefits have also been described for this diet [3], and there are as yet no known health risks.

Low carbohydrate diet

A low-carbohydrate diet is based on a limited carbohydrate intake compared to the average diet. Foods high in carbohydrates are replaced with foods containing a higher percentage of fat and protein (e.g. meat, poultry, fish, shellfish, eggs, cheese, nuts and seeds). There are different degrees of carbohydrate restriction, but a low-carbohydrate diet is considered to be when carbohydrates are restricted to less than 20 % of intake. An extreme form of the low-carbohydrate diet is the ketogenic diet.

Ketogenic diet

The ketogenic diet (KD) is based on a very significant reduction of carbohydrate intake in the diet, replacing it with protein, and above all increasing the intake of fats, which serve as the primary source of energy instead of sugars. In the KD, carbohydrate intake is below 50 grams per day, consisting in the classic form of about 5-10 grams of sugars per day (about 5 % of daily food intake), which is much lower than in low-carbohydrate diets where the carbohydrate intake is reduced to below 20 %.

Ketogenic diets began to be used as a metabolic therapy more than a century ago. The first application was in the treatment of children with refractory epilepsy, where the production of circulating blood ketones due to this diet is able to induce a state similar to prolonged fasting, leading to a reduction in seizure activity. This diet poses no health risks and has great therapeutic potential for specific cases. However, wider use of this treatment methodology has always been hampered by poor long-term compliance [4].

Intermittent fasting

Intermittent fasting has gained huge popularity as a weight loss regime in the last decade. Intermittent fasting is an umbrella term for three different types of diets: alternative daily fasting (ADF), the 5:2 diet, and time-restricted eating (TRE).

ADF is based on alternating a day called a feast day, when individuals eat ad libitum, with a fast day. On the fast day, again, there are two possible types of eating, either intaking water only or consuming about 25 % of energy requirements.

The 5:2 diet is a modified version of the ADF, which includes 5 "feast days" and 2 fast days per week.

The last type is the TRE, which, unlike the previous two, involves restricting food to a certain number of hours per day (usually 4 to 10 hours) and fasting with zero calorie drinks for the remaining hours.

There are a number of studies that demonstrate that these different intermittent fasting regimens are effective for reducing body weight, thereby leading to improved insulin sensitivity, lower blood pressure and markers of oxidative stress in adults with obesity [5].

Health risks are associated with the discomfort that fasting brings. There have been extensive studies from Ramadan fasting, but these data are not entirely generalizable as the normal meal times are altered from day to night during Ramadan, which has a chrono-biological effect that is responsible for some of the negative effects [6]. However, the direct effect of fasting still remains and the results of the studies should be taken as a warning. During fasting there has been described a higher incidence of distracted driving accidents, increased irritability, lower work performance and reduced hours at work [6].

Vegetarian and vegan diets

A vegetarian diet is characterized by the absence of animal products, especially red meat, resulting in a lower intake of saturated fat and cholesterol. The vegetarian diet can be further divided into pesco-vegetarian (the absence of all animal products except fish), lacto-ovo-vegetarian (the absence of all animal products except eggs and dairy products), ovo-vegetarian (the absence of all animal products except eggs) and vegan (the absence of all animal products). Consumption of a vegetarian diet is associated with a number of health benefits, but with long-term consumption there is a risk of deficiencies mainly of protein and thus of some essential amino acids, as well as of some vitamins (B12), calcium, iron and ω-3 fatty acids, which can be prevented by careful monitoring of intake and supplementation [1]. Unfortunately, however, sometimes the fear of deficiency leads to overdoses with industrially produced food supplements in followers of this style, reducing both the health benefits as well as the “naturalness” of this diet. Overdoses are often caused by the misconception that food supplements are only beneficial to health and cannot have adverse effects. It is difficult to diagnose illnesses or feelings of discomfort that arise in this way, and more importantly, it is virtually impossible to explain to followers of this type of diet that it may not be a 'healthy' or ‘natural’ lifestyle. The health risks are therefore linked both to a deficiency of certain essential dietary components and to overdosing on food supplements.

Analysis of the biggest interfering factors

It should be understood that changes in both weight and circadian rhythm are large drivers of steroid hormone concentrations. In order to examine changes induced by diets, we need to exclude the influence of these large effects, otherwise slight changes in these large ones are completely lost or we may even find opposite results. Last but not least, we need to keep in mind the analytical problems in the determination of steroid hormones, which will greatly affect the final results, and also the theory of free and bound steroids and thus the role of changes in binding proteins [detailed in 7].

The effects of weight change

Weight change is a well-known driver of steroid hormone concentrations. A classic example is the effect on testosterone. Obesity leads to a decrease in total testosterone in men by reducing SHBG levels, while free testosterone tends to be normal. This effect should be considered in the diagnosis of hypogonadism, which is common in obese men. Diagnosis and treatment is thus very difficult, precisely by differentiating hypogonadism from physiological changes with weight gain [8]. After weight reduction, there is an increase in testosterone levels, regardless of the type of diet that led to the weight reduction. In women, weight gain leads to an increase in testosterone levels and a decrease in SHBG levels, and may be accompanied by the development of polycystic ovary syndrome (PCOS). One of the six phenotypes of PCOS is indeed characterized by its disappearance after weight loss [9]. In these two examples, it is the weight loss, not the type of diet, that leads to changes in concentration, so it is crucial to exclude this effect in any evaluations and to only consider studies where no weight change has occurred to assess the effect of diet.

Effects of changes in mealtimes

Food intake itself leads to a change in the concentration of steroid hormones. How big this change will be depends on the amount of food, but also the time of day of the meal. First of all, it is necessary to understand the physiological changes of steroids during the day. Most steroid hormones have a clearly expressed circadian rhythm. This is best seen in the changes of cortisol levels, which decrease before falling asleep, with a peak decrease at midnight below 100 nmol/l, followed by an initial rise two hours before waking, then increasing by about 50-70 % in the first 30 minutes after waking and lasting for about an hour, with a subsequent decrease in cortisol during the day and the cycle repeating. It goes without saying that these physiological changes need to be taken into account in studies when scheduling collection times so that any statistical significance is not merely due to circadian variation [7].

Within the circadian rhythm, there is then the added effect of steroid hormone increases induced by food intake [10,11]. This is a system that is maintained by food, but changes are evident at lunchtime even when food is skipped [12]. The relationship between circadian rhythm and food intake is tightly set, and changes in this relationship lead to the development of obesity [13]. The effects of shifting mealtimes as part of various fasts then primarily lead to circadian changes, and trends in hormone concentrations during the day vary depending on the meal skipped [14]. This issue is discussed in more detail below for cortisol, where changes in its circadian rhythm induced by meal shifts are described.

Recent studies also describe negative health consequences caused by circadian rhythm dysregulation induced by changes in meal frequency during the day, both in terms of frequent eating (six or more) and infrequent eating, and a regular diet including breakfast and maximum energy intake early in the day appears to be the most natural [15, for more detail].

Individual steroids and the impact of diets

In the following section, we discuss key individual steroids starting with their main function, site of formation and physiological changes that are key in assessing diet-induced changes. This is followed by a description of the literature data on changes for each diet. In general it can be stated that most studies are hampered by the effects of changes in weight. There are few papers in the literature that describe the actual effects of diet on individual steroid concentrations, and most data are on testosterone. Of the various diets the best described are the effects of vegetarianism/veganism, as these involve long-term changes in diet allowing the effects of these diets to be well monitored. Surprisingly, however, most studies include participants with different BMIs, and a critical approach is needed. There are also relatively more studies on the Mediterranean diet. Other diet approaches lack good long-term compliance, so valid data are scarce. Of particular interest is the issue of compliance related to the relationship between steroid concentrations and diet adherence. The hormonal system is also involved in the setting of taste preferences, which has a decisive influence on the choice and adherence to a specific diet [16]. Thus it is necessary to remember in any general evaluation that the choice of diet influences hormonal levels, but also that hormonal levels influence the choice of diet, in a greatly complex relationship.

Testosterone

Testosterone is the main androgen in humans. Testosterone acts on the development of primary and secondary sexual characteristics, has an anabolic effect on muscle and bone, and in men conditions spermatogenesis in concert with the action of follicle-stimulating hormone. It is secreted in males mainly by Leydig cells of the testis, but some is also produced in the periphery from precursors of mainly adrenal origin. Testosterone levels in men have an early morning peak upon awakening and decline into the evening hours before going to sleep and then rise again. The difference in the amplitude of this process decreases with age, with a very pronounced age dependence. In women, the daily production is 0.1-0.4 mg, with half this amount produced in the periphery by conversion from precursors and the other half produced equally by the adrenal glands and ovary [7]. Female testosterone concentrations change during the menstrual cycle in a similar way to androstenedione, with a periovulatory increase of up to 25 %; this increase is due to an increase in testosterone production in the ovary [17]. Changes during the day are inconsistently described in the literature, and the study by Rácz *et al.* [11] found slight non-significant changes.

Restrictive diets have been shown to decrease testosterone in men. In a large US study looking at the relationship of various diets (low-fat, Mediterranean and non-restrictive) and testosterone, testosterone was significantly lower in the low-fat and Mediterranean diets after excluding the effects of comorbidities, age and BMI [18].

A negative relationship between adherence to the Mediterranean diet and testosterone levels has been described in women with PCOS [19]. This relationship was confirmed in another study comparing women with PCOS and metabolically healthy and unhealthy obesity, with higher testosterone and metabolically unhealthy obesity associated with lower adherence to the diet [20]. Further data on this relationship can be expected soon from the ongoing study by Scannell *et al.* [21].

The relationships between changes in testosterone and other steroid levels associated with vegan/vegetarian diets are the most widely studied. The difference between vegan and vegetarian diets is substantial and it is necessary to distinguish between the different types. Unfortunately, in most papers comparing testosterone levels there are significant differences in BMI between the groups, reflecting around 10 kg in weight. Although patients are mostly in the normal BMI range, the results need to be critically evaluated as the primary differences described are changes in SHBG in terms of higher concentrations in vegans compared to omnivores [22] and even compared to vegetarians [23] or in vegetarians compared to omnivores [24]. The effect on free testosterone is described inconsistently, from decreases to no changes, but these data are virtually impossible to interpret as the lower SHBG groups have significantly higher weight. Another effect on testosterone, that is difficult to interpret, are the results of the study by Schmidt *et al.* [25], where a change to a low fat lacto-vegetarian diet resulted in a decrease in weight after three months in men, but also a decrease in urinary testosterone excretion, which generally does not occur during weight loss. Overall, these data may indicate a trend toward testosterone declines. A very interesting intervention study with a defined diet (vegetarian and western) for two weeks in the same group of men may have supported this, as lower nocturnal testosterone release was found in vegetarian men [26]. Unfortunately the authors did not report an effect on weight, although after two weeks this could not be counted on anyway. The only study in which there was no change in weight and described a difference between a lacto-ovo vegetarian and a mixed meat-rich diet for six weeks in athletes. This study found no effect on free testosterone or SHBG, and only a small decrease in total testosterone in lacto-ovo vegetarians [27]. However, the overall effect of a plant-based diet appears to have little effect on testosterone changes in men, and a study addressing at whether the proportion of a plant-based diet has an effect on testosterone levels did not find an association [28]. This effect is certainly hidden among the larger movers (both age and BMI were significant in the study).

In women, studies have similar problems with weight differences, thus higher SHBG and lower free testosterone are similarly found in vegetarian women, but at lower BMI [29]. Similarly, testosterone was found to decline in postmenopausal women on a fiber-rich diet, but there was also weight loss in this study [30]. A study that accurately describes the situation compared adolescent vegetarian and non-vegetarian women who had normal BMI, did not differ in weight, and in addition described changes during the menstrual cycle [31], and found no difference in testosterone levels during the menstrual cycle. Thus, there are unlikely to be differences in testosterone changes associated with diet in women.

Studies pursuing at the effects of the ketogenic diet in men area clear example of how weight change can confound results. A number of papers describe an increase in testosterone in men on a ketogenic diet [32-36], but all of them show weight loss so these increases are likely entirely the effect of weight change and not the effect of diet type. These papers only confirmed a long-known fact from textbooks of endocrinology that weight loss leads to improved testosterone levels and the disappearance of signs of hypogonadism. Interestingly, the effect of reductions in overweight/obesity is so strong that there can be significant changes despite the influence of diet type, which is the opposite in this case. This is the major contribution of these papers, but otherwise their results should be interpreted more cautiously than indicated in their titles. Those papers do provide evidence that the ketogenic diet is appropriate even in obese men with hypogonadism. What direct effect the ketogenic diet has is shown by other papers where there was no change in weight, where it was shown that a ketogenic diet compared to a Western diet leads to a decrease in testosterone levels in men [1, 37]. The same results, i.e. a significant decrease in testosterone, have been found with a low carbohydrate diet [38].

Studies addressing at the effect of ketogenic diets in women have been devoted to changes in testosterone in the context of PCOS. Some have found decreases in total and free testosterone in women with PCOS with significant weight loss [37, 39], with similar findings with low carbohydrate diets [4]. Great caution is also in order here in interpreting the results as a treatment for PCOS, as the true effect on testosterone levels is not precisely revealed. Certainly, if a diet leads to weight loss and thus a reduction in testosterone levels despite direct effects being unknown, this is evidence of its suitability. The above-cited papers also showed little compliance with completing the diet, which may be evidence that this type of diet in women with PCOS leads to only minor dietary changes. This may certainly be linked to the hypothesis of a role for testosterone in adherence to this type of diet, as already described for the Mediterranean diet. And one can only speculate on the actual effect of ketogenic diets on testosterone levels in women, with all directions possible - no effect, decreases or increases.

The results of the study by Molteberg *et al.* [40] dealing with at the effect of a 12-week ketogenic diet on patients with resistant epilepsy are very difficult to interpret regarding steroid hormones, as the study was preferentially focused on assessing bone markers. They found unchanged total testosterone levels, a decrease in free androgen index, and an increase in SHBG in both sexes. There was a significant decrease in weight in the study, although only by 1.8 BMI points. The major limitations of the study for evaluating steroid hormones are the large age variance, BMI variance, and most importantly the small number of participants enrolled, due to the necessity of sex distribution. The results suggest that the change in SHBG is early and precedes the change in total testosterone. Similar results were found in our work following males who quit smoking [41], but it is possible to speculate whether this is just a weight loss effect or whether the type of diet is also involved.

A time-restricted (TRE) dietary regimen (16/8) for 8 weeks resulted in a decrease in testosterone in healthy men who regularly exercised compared to a similar group of men on a normal diet where no change occurred, while at the same time there was a decrease in body fat in TRE without further changes in body composition [42]. The same research group confirmed this at the one year follow-up, where TRE (16/8) still resulted in a decrease in total testosterone compared to those on a regular diet, as well as an overall spontaneous decrease in energy intake [43]. Furthermore, the authors looked at changes in top cyclists on a TRE (16/8) diet lasting 4 weeks and demonstrated a reduction in free testosterone [44]. Another research group studied the effect of four weeks of intense exercise plus TRE (16/8) or a normal diet, and in both groups, they found a decrease in testosterone but also a decrease in body mass, fat mass and fat percentage [45]; here the effect may be due to a decrease in total body mass.

In a small study looking at the effect of a TRE diet (4-6 hour eating window) for eight weeks in both fertile and postmenopausal women, testosterone was unchanged despite a decrease in weight. There was also no change in SHBG [46]. Changes in overweight/obese women have been described for free androgen index or SHBG with 5:2 or TRE diets, but as there was always a significant change in weight [5], these changes need to be assessed critically.

Interestingly, a study by Jakubowicz *et al.* [47] compared dietary time change in overweight women with PCOS. Shifting 50 % of calories to breakfast time versus shifting 50 % to dinner time resulted in a decrease in free testosterone and an increase in SHBG without a change in weight.

Estradiol

Estradiol is the most potent endocrine estrogen and, together with progesterone, controls female reproductive processes. In addition to reproductive functions, estradiol plays a significant role in bone, muscle and adipose tissue metabolism [7]. During fetal development it is responsible for the sexual differentiation of the brain, with the male brain developing in its presence and the female brain in its deficiency [48]. Estradiol is produced by the follicles of the ovary of sexually mature women mainly around ovulation, during pregnancy and by the placenta, and is also produced in small amounts by the adrenal glands. In males, small amounts of estradiol are produced by the testis and adrenal gland [7]. Estradiol has a clearly expressed circadian rhythm, with a morning peak [49] and a nighttime acrophase [50], and rhythmic shifts within the menstrual cycle [49,50].

A reduction in urinary estrogens has been described in postmenopausal women on the Mediterranean diet for six months compared to a traditional diet [51]. In contrast, in a study addressing at dietary patterns in relation to estrogen concentrations in postmenopausal women, no relationship with the Mediterranean diet was found [52]. However, the results should be interpreted with caution, as the authors in both studies sought to look for dietary factors that reduce estrogen levels and thus the possible prevention of breast cancer. Studies designed in this way are relatively common in the literature, but the very complex design of the various associations is not useful for assessing hormone levels alone.

The effects of vegetarian diets in men were described in just one study where the condition of unchanging weight was observed. There were no changes found in either estradiol or estrone between groups after six weeks of a lacto-ovo vegetarian diet versus a varied meat-rich diet in athletes [27].

In women, studies have faced problematic assessments in the context of differences in body composition. This was exquisitely demonstrated in a large study by Thomas *et al.* [53] comparing differences between meat-eating, vegetarian and vegan women. The authors showed that the finding of higher SHBG and lower estradiol in vegetarian and vegan women disappeared after adjusting for BMI.

Interesting in this regard are the results of the intervention study, in which participants in the study did not change weight. The intervention was conducted in women who routinely ate meat before entering the study, and changed to a vegetarian diet and a vegetarian diet plus fish for 3weeks. The womens' SHBG levels appeared to be negatively correlated with fat intake, but there was also a decrease in estradiol on the vegetarian diet; there was no change on the vegetarian plus fish diet [54]. Opposite changes in estradiol have been demonstrated in a study comparing adolescent vegetarian (from a Seventh-day-Adventist church) and non-vegetarian participants, in which the subjects did not differ in weight, had normal BMI, and changes were also described over the menstrual cycle. The study found higher levels of log follicular estradiol in vegetarian women [31]. A similar study comparing premenopausal women (again of the Seventh-day Adventists) and non-vegetarian women showed lower estradiol and estrone in vegetarian women, with estradiol and estrone levels positively correlated with linoleic acid and protein intake [55]. Similarly, another study in postmenopausal vegetarian and non-vegetarian women showed a decrease in estradiol in vegetarian women [56]. There may be an effect of age, where the changes may apply inversely, but also an effect of the overall duration of the diet.

In the ketogenic diet, unchanged estradiol levels regardless of age have been described in both men and women after 12 weeks of dieting with a significant but small decrease in weight [40]. The wide age and BMI variance with a small number of probands (total male and female n=52) limitation the accurate interpretation of sex hormone assessments in this study`, and their follow-up was only marginal, as the study focused on bone metabolism in patients with refractory epilepsy and here their data are very useful.

Li *et al.* [57] described a reduction in estradiol after 12 weeks of a ketogenic diet in obese women with PCOS, but with a significant reduction in weight that resulted in the modification of metabolic parameters. The second major limitation of the study is the comparison with a control group that received hormonal contraception. Although there was no difference between the groups in estradiol, the data collected while using contraceptives is no longer interpretable; it is one of the basic exclusion criteria for evaluation due to changes in binding proteins.

In a small study pursuing at the effect of a TRE diet (4-6 hour eating window) for eight weeks in postmenopausal women, estradiol and estrone were unchanged despite weight loss [46].

Progesterone

Progesterone is the most important gestagen. In women, it is secreted by the ovary at various levels depending on the menstrual cycle, most abundantly postovulatory from the corpus luteum under the influence of LH. Its function is the preparation and maintenance of pregnancy. It is also produced to a small extent in the adrenal cortex or, in men, in the testes. There is little information on the function of progesterone in men, although its levels do not differ from those in women in the follicular phase of the cycle. Progesterone influences spermatogenesis, sperm capacitation and testosterone biosynthesis in Leydig cells. In both sexes, it has effects on the central nervous system (mainly mediated by 5α-reduced progesterone metabolites), including the inhibition of gonadotropin secretion, effects on sleep, and a protective response to brain ischemia or trauma. It also has effects on the immune system, cardiovascular system, renal function, adipose tissue, behavior and the respiratory system. Progesterone exhibits a pronounced circadian rhythm with a decrease during the day [11] and differences during the menstrual cycle with disappearance in the luteal phase [50].

In overweight women with PCOS, a ketogenic diet led to an increase in progesterone [37], but there was also a decrease in weight on the diet, so the results for this and other hormones should be interpreted with caution. In another study in women on PCOS and metabolic risks, the effect of a ketogenic diet and conventional therapy (Essencialle and Yasmin) was compared, and both groups showed a decrease in progesterone with no difference between the groups [57]. The study was primarily focused on metabolic parameters where the positive effect of diet was demonstrated, but the protocol is completely inappropriate for evaluating hormonal. The primary therapeutic effect of hormonal contraceptives is to shut down cyclical changes in sex steroids within the menstrual cycle and alter their levels, and to compare this with the effect of diet is not appropriate. In addition, hormonal contraceptives can cause major interference in the laboratory analysis.

In a small study looking at the effect of a TRE diet (4-6 hour eating window) for eight weeks in postmenopausal women, progesterone was unchanged [46].

Cortisol

In humans, cortisol is the most potent hormone of the glucocorticoid group produced by the adrenal cortex. Its secretion is stimulated by ACTH and inhibited by feedback. Cortisol plays a major role in the body's response to and management of stressful situations (stress, infectious diseases, great physical exertion, prolonged starvation). Its basic effect on metabolism is catabolic. In the liver, however, it has an anabolic effect and increases gluconeogenesis. Cortisol possesses a distinct circadian rhythm with a maximum in the morning and a minimum in the evening [7].

Similar to testosterone, higher levels of salivary cortisol are associated with lower adherence to the Mediterranean diet [58]. Similar results were shown in a study addressing at the relationship between dietary choices and changes in the hypothalamic-pituitary-adrenal axis (HPA axis). Women who chose a diet similar to the Mediterranean diet had lower levels of disturbances to the HPA axis [59].

Studies pursuing at the effect of the Paleolithic diet on corticoid metabolism have shown just that weight loss leads to its improvement even on this diet [60,61]. What the effect of this diet is on hormone levels cannot even be speculated.

A study dealing with at altering the stress response on a ketogenic diet found a reduction in salivary cortisol and improvements in metabolic and anthropometric parameters in obese men [62]. The study was not primarily aimed at monitoring hormonal levels, and it is apparent that generalizations of the findings cannot be applied due to the dominant effect of weight change. Furthermore, a reduction in cortisol-binding globulin and changes in 11βsteroid dehydrogenase of both types in visceral fat, which are responsible for the change from cortisol to cortisone and back again, have been described in ketogenic diets [63].

A study comparing the effect of exercise and TRE (16/8) compared toa normal diet found an increase in cortisol in only the normal diet group [45]. A meta-analysis of studies in the obese failed to show changes in cortisol with TRE diets, with the authors citing large bias for all parameters studied [64].

Circadian rhythm is typical for cortisol. Dietary changes in terms of meal shifts lead to changes in the daily cortisol profile. In the obese, an improvement in cortisol rhythmicity has been described with TRE (fasting 10 h from 19.30) after eight weeks, with a decrease in morning cortisol area under the curve and without a decrease in evening cortisol [65]. Skipping night meals is very positive for circadian rhythms and is the first step to improving metabolic status in the obese. The changes induced by shifting mealtimes within the day were the focus of a meta-analysis that aimed to compare the effect of changes in traditional TRE and dietary changes during Ramadan. Changes in Ramadan are inconsistently described in the literature, with mentions of disturbed circadian rhythmicity, changes similar to those seen in shift workers, but also the preservation of rhythmicity but with a biphasic pattern. In classic TRE, it makes a difference whether breakfast or dinner is skipped. With dinner skipping there is a decrease in evening cortisol and a nonsignificant increase in morning cortisol. Conversely, when breakfast is skipped, there is a significant decrease in morning cortisol [14].

Significant increases in cortisol have been described for fasting (3-30 days) with more pronounced changes for prolonged fasting [66].

Dehydroepinadrosterone

Dehydroepiandrosterone (DHEA) is sometimes confused or even misattributed in the literature with its sulfate (DHEAS), from which it differs and even has some opposite functions. In the past it was considered an insignificant intermediate of steroid metabolism, but gradually its importance is becoming apparent, particularly due to its action in the brain, where it is produced next to the adrenal glands and binds to GABAA calcium channel receptors, thereby affecting some psychological functions. The site of about one half of its production in women is the adrenal glands, the other half is secreted by the ovaries or is formed by the conversion of the sulfate form in the periphery. The course of DHEA concentrations during life is similar to that of its sulfate. But unlike DHEAS, DHEA has a clearly expressed diurnal profile that mimics that of cortisol. Changes during the menstrual cycle are minor with a slight increase in the late luteal phase [67].

Difference in DHEAS concentrations between vegans and men who eat meat were not demonstrated in the study by Belanger *et al.* [24], and even in this study there was a change in weight.

In a small study looking at the effect of a TRE diet (4-6 hour eating window) for eight weeks in both fertile and postmenopausal women, there was a decrease in DHEA with a weight loss of around 3-4 % [46].

Dehydroepinadrosterone sulfate

Dehydrepiandrosterone sulfate is the major adrenal androgen and the most abundant steroid hormone ever produced in terms of quantity. DHEAS is produced directly as a sulfate, and is found in the blood in high micromolar concentrations, several orders of magnitude higher than other steroid hormones, whose concentrations are nanomolar [68]. Many studies have described its influence on a number of metabolic processes. It is only slightly androgenic, but may serve as a precursor of androgens and estrogens in the periphery. DHEAS is also active as a neurosteroid. Its physiological levels are age and sex dependent, but levels do not change significantly during the day or within the menstrual cycle. It is an adrenal steroid so we would expect changes during the day, but it is possible that due to high concentrations, slight changes during the day have not been detected [67]. In the study by Rácz et al [11] some small changes were found in relation to time of day and food.

A very interesting study of dietary intervention in relation to DHEAS is the follow-up of a group of twenty-six healthy centenarians (aged 100-105 years) from Italy who ate a Mediterranean diet and had moderate alcohol intake (up to 500 ml of red wine per day) throughout their lives. Changing the diet in the last year led to a reduction in DHEAS levels, changing the diet and abstinence in the last year led to an even greater reduction in DHEAS, and the same effect was seen on IGF-1 levels [69]. That study demonstrates the suitability of the Mediterranean diet even with moderate alcohol consumption and the inappropriateness of changing this diet, especially for centenarians.

In the only study where the condition of unchanging weight was maintained, changes in DHEAS in male athletes on a vegetarian diet were also monitored. They did not demonstrate changes, as DHEAS did not differ between groups after six weeks of a lacto-ovo vegetarian diet versus a varied meat-rich diet [27]. Similarly, differences in DHEAS between vegan and meat-eating men were not demonstrated in the study by Belanger *et al.* [24], and weight change also occurred in this study. A short-term effect (five days) of a lacto-vegetarian diet on adrenal function was shown in a study in which, however, there were only six volunteers, and the effect is therefore influenced by the small number of subjects (only one in the lacto-vegetarian group). The authors mention an increase in plasma and a decrease in urinary DHEAS and speculate on a decrease in adrenocortical activity [70]. Higher DHEAS in the luteal phase has been described in vegetarian adolescents compared to non-vegetarian women in a study that respects the phases of the cycle and had no difference in weight between the groups [31].

Ketogenic dieting and partial fasting for seven days led to an increase in DHEAS in patients with rheumatoid arthritis, with a significant change in weight of around 3 kg [71]. In overweight women with PCOS, ketogenic dieting led to a decrease in DHEAS [37], but in that study there was a decrease in weight on the diet, so the results on that and other hormones should be interpreted with caution.

Androstenedione

Androstenedione is a weak androgen and a direct precursor of testosterone in the gonads and estrone primarily in adipose tissue. In women, the level of circulating androstenedione varies during the menstrual cycle similar to that of testosterone, increasing by about 25 % during the periovulatory period. At the same time, it has a circadian rhythm. A slight decrease in androstenedione is described with age, but after menopause it remains the main steroid hormone of the ovary [7].

Changes with a vegetarian diet are described in male athletes for androstenedione in one study where the condition of unchanging weight was observed. The study showed no changes, as androstenedione did not differ between the groups after six weeks of a lacto-ovo vegetarian diet versus a varied meat-rich diet [27].

Potential mechanisms

Testosterone metabolism and ketone bodies

The decrease in testosterone in men following a ketogenic diet without weight loss, as well as the lower testosterone in intermittent fasting, leads to a possible hypothesis for the role of ketone bodies in testosterone metabolism. In an experimental model in male rats, ketones induced testosterone 2 β- and 6 β-hydroxylase activities in the liver, with the extent of induction depending on the length of the ketone side chain [72]. Influencing testosterone levels in the sense of increasing its metabolism by ketone bodies could be one possible mechanism explaining lower testosterone levels in the ketogenic diet. Likewise, influences within cytochrome P450. It might then be suggested that even in women on a ketogenic diet, testosterone levels would be reduced and the diet would be suitable for women with PCOS, but we have no evidence for this. It is important to note that the mechanisms of action tend to be different between the sexes, generalizations cannot be easily made, and in women the interference with testosterone metabolism may be at a different level.

Steroids and fiber

In the literature, reductions in the levels of some steroids described in vegetarian/vegan diets has been related to changes in enterohepatic steroid circulation and higher steroid excretion due to a higher proportion of dietary fiber [73-75]. Estrogens correlate positively with the amount of fat in the diet and negatively with the amount of fiber [76]. The type of diet can influence not only metabolism directly but also excretion.

Testosterone and adherence to diet

The question of testosterone levels and diet adherence in women with PCOS seems perspectively interesting, and in addition testosterone levels could potentially be altered. In women with PCOS, a negative relationship between adherence to a Mediterranean diet and testosterone levels has been described [19], this relationship was confirmed in another study comparing women with PCOS and metabolically healthy and unhealthy obesity, but even there higher testosterone and metabolically unhealthy obesity was associated with lower adherence to the diet [20]. Further data on this relationship can be expected soon from the ongoing study by Scannell *et al.* [21]. Studies looking at the effect of ketogenic diets [37,39] or low carbohydrate diets [4] have had similarly low adherence. These findings can be linked to the hypothesis of a role for testosterone in adherence to the type of diet as already described for the Mediterranean diet. This points to a complex relationship between dietary intake and steroids, with diet influencing steroid levels, but steroids also influencing diet choice and/or adherence. This is similar to changes we found in smokers, where smoking both altered steroid hormone levels, but at the same time steroid hormones played a role in maintaining tobacco dependence [41,77-80].

Conclusion

The most significant dietary-related changes are found in testosterone in men, with reductions in levels with ketogenic diets and other restriction regimens. Changing the time of day of meals leads to changes in circadian rhythm hormones, as has already been documented for cortisol, with possible health consequences. As described for testosterone in women with PCOS, hormone levels lead to different adherence to a given type of diet. The best option for a healthy diet, also in terms of hormone levels, is a regular diet with three meals a day (with most food taken rather in the first half of the day) and a varied diet, not highly processed, with adequate energy intake and nutrient distribution. For some patients a change of diet is certainly indicated as part of therapy (e.g. ketogenic diet in resistant epilepsy). While in this particular case side effects are minimal, it must be kept in mind that every treatment has possible side effects, and this is not a generally recommended procedure for healthy people.

Dedication

This article is dedicated to my supervisor Prof. Stárka [81], who brought me to the topic of steroid hormones and with whom I had the opportunity to collaborate on this beautiful topic for twenty years. It was a wonderful time full of interesting discussions and great collaboration. Miss you, professor.

Conflict of Interest

There is no conflict of interest.

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