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Hypercholesterolemia treatment: a new hypothesis or just an accident?

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Summary A new hypothesis concerning the association of low levels of steroid hormones and hypercholesterolemia is proposed. This study presents data that concurrent restoration to youthful levels of multiple normally found steroid hormones is able to normalize or improve serum total cholesterol (TC). We evaluated 20 patients with hypercholesterolemia who received hormonorestorative therapy (HT) with natural hormones. Hundred percent of patients responded. Mean serum TC was 263.5 mg/dL before and 187.9 mg/dL after treatment. Serum TC dropped below 200 mg/dL in 60.0%. No morbidity or mortality related to HT was observed. In patients characterized by hypercholesterolemia and sub-youthful serum steroidal hormones, our findings support the hypothesis that hypercholesterolemia is a compensatory mechanism for life-cycle related down-regulation of steroid hormones, and that broadband steroid hormone restoration is associated with a substantial drop in serum TC in many patients.

INTRODUCTION

Atherosclerotic cardiovascular disease (ACVD) is the greatest cause of death among adults in the United States. Elevated TC is closely linked epidemiologically and causally to ACVD (1). There are many treatment guidelines for hypercholesterolemia in North America and Europe (2). In coronary heart disease (CHD), the most benefit with lipid-lowering therapy is observed in patients with hypercholesterolemia evidencing ischemia (secondary prevention) (3). Drug intervention intended to decrease cardiovascular risk before an initial cardiovascular event (primary prevention) is controversial (4). Treatment of hypercholesterolemia with lipid-lowering drugs reduced ACVD events, but adverse events (24%) and quality of life morbidity indicates the need to find better regimens for elevated TC (5,6). The concept of quality of life adjusted survival has developed in many areas of medicine to address an increasing awareness that survival alone, while easily measured, should not be the sole determinant of superiority in assessing interventional therapies. However, no guidelines encompass the effects of interventions, which decrease risk of CHD indirectly and which do not act specifically to alter blood lipid metabolism (7). In spite of the decreasing trend in age-adjusted cardiovascular mortality, an increase in cardiovascular morbidity is projected due to population ageing (8). Aging is regularly associated with a decline in serum levels of multiple steroidal hormones and often associated with intercurrent life threatening lipid disorders. Some studies of estrogen–androgen therapy have reported reduction in serum levels of TC, triglycerides, LDL, and HDL (9,10). Even though a few studies describe a 25–44% reduction in CHD following estrogen therapy with or without progestogen, the role of such hormone replacement therapy (HRT) in the prevention of ACVD in women remains controversial (11–13). Recent findings of the Heart and Estrogen/Progestin Replacement Study trial found no overall reduction but even (rather) an increase in coronary events among women assigned to active hormone treatment (14). While evidence that dehydroepiandrosterone (DHEA) will lower TC and LDL has been presented (15), other studies have failed to confirm this finding (16,17).

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We proposed a hypothesis for hypercholesterolemia: steroidopenia, as a consequence of aging, is causal to most hypercholesterolemia related clinical disease. This hypothesis implies hypercholesterolemia to be the reactive consequence of the age related, enzyme dependent, down-regulation of steroid hormone synthesis and interconversion. Based on this hypothesis, we focused our attention in this study on determining the importance of the multiple hormone restoratation in reduction of hypercholesterolemia. We failed to find reports in the medical literature of an association between simultaneous restoration of multiple steroid hormones to youthful levels and major reduction in TC.

PHYSIOLOGICAL PURPOSE OF HYPERCHOLESTEROLEMIA

Of all the risk factors in ACVD, age is the most powerful. Andropause and menopause consist of the natural life cycle cessation of cyclic gonadal function and mark the end of natural protection against CHD. Before these age dependent changes, CHD is infrequent suggesting steroid hormones may offer protection. A number of studies have shown that postmenopausal women on hormone therapy have reduced risk of CHD (18). A previous meta-analysis of trials of HRT also shows net harm (19). Less clear is the CHD benefit of testosterone or other steroidal hormones in andropausal men (20).

Adrenal and gonadal steroids are derived from cholesterol (Fig. 1). As we age, deleterious changes occur in the servomechanisms of body systems to compromise health. These progressive and cumulative aberrations of homeostasis are to a major extent predictable. Target organs may become less sensitive to their controlling hormones or cell membrane receptors may break ligands down at slower rate leading to decreased effect. Aging is regularly associated with serologic depression in multiple steroidal hormones and is often associated with life threatening lipid disorders as well. Multiple enzymatic processes convert cholesterol first to pregnenolone and then to several other derivative steroids. Protein neogenesis, including fabrication of most proteins constituting enzymatic systems, seems to regularly down-regulate with aging. Age related changes in anabolic and catabolic hormones work like one mechanism to produce the clinical endpoints of disease. As failed enzyme anabolism and failed lipid catabolism becomes more dominant, our body will progressively accumulate excessive cholesterol.

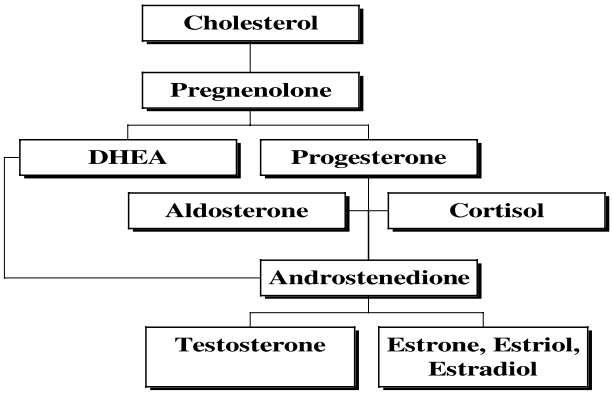

Fig. 1 Simplified version of cholesterol metabolism.

We suggest our own hypothesis for hypercholesterolemia and its treatment, which we call the hormonodeficit hypothesis of hypercholesterolemia. According this hypothesis, most hypercholesterolemia and its clinical consequences arises as a feedback or servomechanistic reaction to age-related decline in steroid hormone production. Cholesterol is the building block for most steroid hormones. Decreasing hormonal production induces compensatory increasing production of cholesterol through multiple feedbacks which collectively effort to restore normal youthful homeostasis by precursor loading of synthetic pathways with cholesterol. Cholesterol participates in many vital cell functions and serves as precursor for steroid hormones. Thus, we hypothesize that physiological purpose of hypercholesterolemia in this situation is to serve as a compensatory mechanism to life cycle related down-regulation of one or more steroid hormones. This explanation helps explain why drugs which impair the natural production of cholesterol, might be fraught with adverse health consequences. Such drugs might be expected to regularly decrease the production and serum levels of steroid hormones (21,22). Suppression of hypercholesterolemia, the body's compensatory effort to sustain steroidogenesis in the face of failing synthetic pathways in aging, may induce rapid psychological, somatic, and immunologic deterioration, including low immunoresistance to cancer and infections and acceleration of the aging process with clinical constellations of noncardiovascular disorder (23,24). Rash, gastrointestinal complaints musculoskeletal pain and elevations in liver transaminase levels were the most common reasons for patients withdrawing from these drugs (25,26). The adverse consequences would be expected to be equally deleterious when cholesterol is wasted out of the gut by cholesterol binding agents instead of being recycled for production of steroid hormones.

CLINICAL EVIDENCE

The patients described in this study were not preselected based on lipid disorder; they sought either anti-aging treatment (18 patients) or received anti-aging intervention as a part of integrated cancer care (two patients).

The patients did not have healthier life style or received anti-aging interventions. Patients at presentation were usually evaluated with a steroidogenesis profile starting at its origin with cholesterol, and serial TC determinations were made during treatment.

We analyzed 20 consecutive patients with hypercholesterolemia. Between July 1997 and August 2001, 11 male and 9 female patients were treated with the mean age of 59.0 years (age range 45–80 years). Lipid profile or serum TC, pregnenolone, dehydroepiandrosterone sulfate (DHES), progesterone, total estrogen, and total testosterone levels were determined. Patients received HT with hormones chemically identical to human hormones and administered in physiologic ratios and with dose schedules intended to simulate natural human production cyclicity. The HT agents were oral pregnenolone and DHEA, and cutaneously applied triestrogen (estriol 90%, estradiol 7%, and estrone 3%), progesterone, and testosterone gels. The design of this study was not traditional. No standard dose or rigid protocol was used in our study, because all of the patients needed individualization of dosage according to their blood tests. Dose recommendations to different patients during HT were quite different and were determined by serum hormonal levels during serial testing. Doses were individually modified during HT to produce youthful physiologic serum levels. We titrated doses to achieve the hormonal blood levels of young adults between the age of 20 and 30 for both genders at which time the highest level of all steroid hormones naturally occurs. This level is at the high end of the normal range from the testing laboratory.

Sixteen patients (80.0%) had been taking from one to three different replacement hormones prior to HT. In spite of hormonal replacement patients had a high level of TC before our treatment regimen. All agents such as equine conjugated estrogens, medroxyprogesterone acetate, methyl testosterone, etc. were unnatural to human physiology and were changed. In patients with unphysiologic replacement, such as estradiol alone, physiologic estrogen ratios were restored. Estrogen was always opposed with progesterone. The follow up period was from 2 months to 4.1 years.

All patients (100%) responded to HT (Fig. 2). Serum TC fell to below 200 mg/dL in 12 patients (60.0%). Eight patients still have serum TC levels slightly higher than normal. All of these patients still exhibit a failure of intervention to establish complete normalization of hormonal levels (two cases had persistent pregnenolone deficiency, two cases had DHES deficiency, one case exhibited testosterone deficiency, two instances of deficiency of both testosterone and DHES and one, testosterone and pregnenolone). However, all of these patients had a beneficial drop in TC, which was significantly reduced while staying in the dangerous range before therapy. The highest level of TC after treatment was 226 mg/dL. Mean serum TC before treatment was 263.5 and 187.9 mg/dL afterwards with an average reduction of 28.7%. The drop was from 269.2 to 182.6 mg/dL (32.2%) in men and from 256.6 to 194.3 mg/dL (24.3%) in women. During follow up no patients exhibited complications or side effects related to HT. Most patients described marked quality of life improvement.

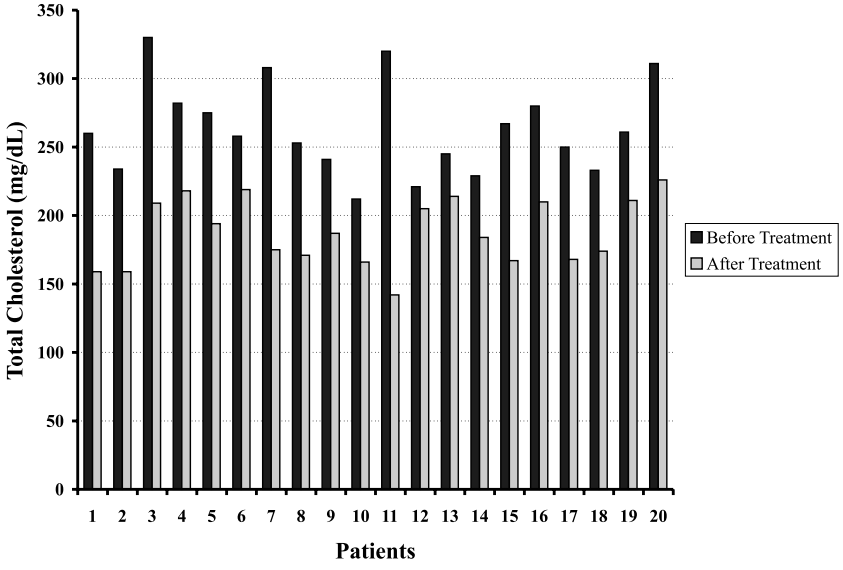

Fig. 2 Total cholesterol before and after hormonorestorative therapy.

CLINICAL IMPLICATIONS

We have tried to manage the clinical problem of hypercholesterolemia using a non-traditional perspective. Not only did HT appear to be much safer than approaches, which pharmacologically obstruct cholesterol synthesis, but also HT was regularly associated with an improved quality of life. Our hypothesis is firstly confirmed by our observations during HT of serum cholesterol decline associated with markedly improved symptoms. Our hypothesis is secondly confirmed by the marked increase during treatment with conventional cholesterol-lowering drugs of the same constellation of aging disorders, which resolve during HT.

Some of the retrospective studies demonstrate that patients with normal level of cholesterol have same frequency of presentation with myocardial infarction as patients with recognized hypercholesterolemia. It has been shown that 45–60% of patients with admissions for myocardial infarction had a 'normal level' of cholesterol (27,28). What is the explanation? According our hypothesis, almost everyone experiences a life cycle related relative elevation of cholesterol level (except of people with congenital enzymes problem) after age 40 when the production of derivative hormones starts to markedly decline even with compensatory adjustment. In our opinion, TC elevation over time in comparison with an earlier base level in the same patient should be a critical determinant and would possibly be far more important in assessing ACVD risk than quantification of absolute TC. This could explain why many people who have a normal level of cholesterol experience heart attacks and present in equal numbers as patients with hypercholesterolemia. The use of anticholesterolemic agents reduces atherosclerotic disease, but patients regularly experience a depression in quality of life. Insomnia, obesity, fatigue, impotence, cognitive clouding, anxiety, psychological depressions may all be related to a decline in pregnenolone, DHEA, and gonadal hormones (29,30).

In our study we employed a novel explanation for hypercholesterolemia and investigated a novel method of pharmacologic intervention based on this explanation to address the risks implicit in the elevated cholesterol. In our opinion cholesterol is one of the best markers of aging and can be used, as a useful instrument in assessing at which time a patient needs to initiate HT. Hypercholesterolemia is evidence of a malfunction in our basic homeostasis. We suspect that evidence of TC rise, even in the normal range (relative hypercholesterolemia), especially in the face of steroidopenia, is adequate justification for exogenous restoration of youthful hormonal profile. Adequate levels of the steroid hormones, such as pregnenolone, DHEA, progesterone, estrogens, testosterone, cortisol in an appropriate balance are necessary for maintaining optimal health in both females and males. This group of steroid hormones supports a wide range of essential physiological functions. Alteration in these hormones plays a large role in the changes observed in life cycle processes during aging.

In our study patients received HT with natural hormones such as pregnenolone, DHEA, triestrogen gel, progesterone gel, testosterone gel, and hydrocortisone. We did not use synthetic hormones. The human body contains all the enzymes and cofactors it needs to process natural hormones when they occur in their natural human proportions and human body metabolizes synthetic hormones significantly less efficiently. In our opinion, inadequate restoration of hormonal profile involving any of several steroids or any kind of hormonal dysbalance may cause of suboptimal restoration of cholesterol level. We believe that much of the controversial reports in the literature related to hormone replacement result from inadequate restoration, as authors failed to employ 'natural' hormones in the proper manner, and persistent aberrations of physiology resulted. Different studies showed controversial results with using estrogens, progestogens, androgens and DHEA for correction lipid disorders (31,32). Unfortunately, the use of hormones for so-called HRT (mostly, estrogen replacement therapy) is done empirically, with one or two standard doses being given to all women without regard for a wide range of individual variability in absorption and metabolism.

We have no uniform treatment protocol, because the best treatment program for one individual may be totally wrong for another. Safe correction of hypercholesterolemia is possible if careful attention is paid to restoration of a youthful hormonal profile. We think that most failed treatment of hypercholesterolemia by HRT arise because hypercholesterolemia is a consequence of a complex of interactions related to steroid metabolism which are not be corrected by only one or two hormones. Recognition of normalcy sufficient to down-regulate cholesterol production requires multiple hormonal interventions, and the hormones must be natural. A primary difference between HT and conventional therapeutic approaches to the problem of hypercholesterolemia is that we do not try to directly decrease the level of cholesterol. The therapeutic decrease is induced indirectly and automatically after restoration of youthful levels of basic steroid hormones. First of all, it was impossible to use placebo-controlled and double-blinded methods in our study, because main purpose (decrease TC level) must be reached through the intermediate goal (restoration youthful level of hormones), and therefore traditional scientific approach makes no sense. Second, because no one has ever used similar approach for correction of

hypercholesterolemia, we decided that it is extremely important to share our results immediately with our colleagues. Numerous conventional societies and big institutions can criticize us for not-traditional scientific approach in this study, but no one can reject that this is an absolutely different point of view on the hypercholesterolemia treatment. We did not give detailed information and did not make analysis of hormonal level, because of the different purpose of this study. This information is not insufficient. We did not want to lengthen the paper, and only mentioned that level of most hormones after treatment was close to maximal lab references for youthful range. We are not talking today about different length of follow up or the age range of the studied subjects. We are talking about the new approach with unusual response of TC to our intervention. Once again, we realize that we did not follow the traditional rigid scheme of study, and just presented our hypothesis and the findings, which indicate that HT in hypercholesterolemia can produce major reductions in cholesterol.

We do not suggest a panacea for treatment of all cases of hypercholesterolemia, but our approach to the understanding and treatment of hypercholesterolemia may provide the means for intervention in many situations. We hope that it will serve as the basis for further improvement in quality of hypercholesterolemia management.

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