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DHEA and Impaired Glucose Tolerance Clinical and Basic Study

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1. Introduction

Dehydroepiandrosterone (DHEA) is either secreted directly from the adrenal cortex or is converted from DHEA sulfate (DHEA-S) in the peripheral organs. DHEA and DHEA-S are the most abundant adrenal androgens in blood, however their its physiological roles still remain unclear. Some recent studies have shown that DHEA and DHEA-S exert beneficial effects on conditions such as diabetes mellitus, atherosclerosis, obesity, tumors and osteoporosis (Coleman et al.,1982; Gorden et al.,1988; Cleary,1991). In this chapter, the relationships between DHEA or DHEA-S and diabetes mellitus (DM) or impaired glucose tolerance (IGT) are described.

2. Clinical and basic study

2.1 Clinical study

Abnormalities of secretion and metabolism of many steroid hormones occur in DM. In poorly controlled type 1 DM, serum concentrations of DHEA and DHEA-S decrease (Couch,1992) while plasma ACTH and cortisol levels increase in type 2 DM (Hashimoto et al.,1993). Low levels of DHEA and DHEA-S in type 2 DM are associated with hyperinsulinemia(Hubert et al.,1991; Nesler et al.,1989; Schriock et al.,1988; Smith et al.,1987;). We analyzed serum DHEA and DHEA-S levels in poorly controlled type 2 DM.

2.1.1 Subjects and methods

The subjects were type 2 diabetic patients seen regularly at the outpatient clinic of Toho University Hospital. We chose 130 patients, whose blood glucose control had been poor (more than 10% in HbA1c). Their medication was managed by diet only or with sulfonylurea, and patients under insulin therapy were excluded. The patient group consisted of 74 men and 56 women between the ages of 40-69yr. Age-matched normal subjects served as the control group. Informed consent was obtained from each subject before the study.

Blood samples were obtained from patients with type 2 diabetes mellitus and normal subjects between 9 and 10 a.m. after an overnight fast. From patients with type 2 diabetes mellitus, blood samples were obtained before and 6 months after the treatment. Serum levels of DHEA, DHEA-S and immunoreactive insulin (IRI), fasting plasma glucose (FPG) and HbA1c were measured. Steroid hormones were determined by the previously reported

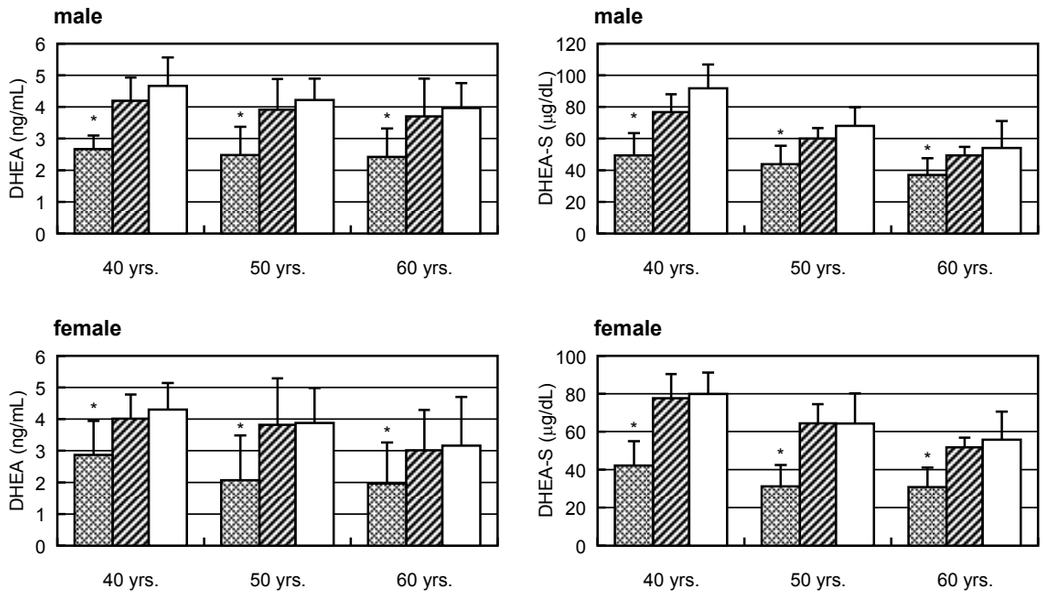
HPLC/RIA method(Ueshiba et al.,1991) except DHEA-S which was measured using RIA kit(Mitsubisi Chemical Co., Tokyo, Japan), FPG by glucose oxidase method, HbA1c by HPLC, IRI by commercial kits (Daiichi, Tokyo, Japan). Data are showed as mean ± SD. Variables were compared by Bonferroni's analysis and p-values less than 0.05 were considered to indicate statistical significance.

2.1.2 Results

Serum levels of DHEA and DHEA-S were low in both male and female patients with type 2 DM across the entire age range studied, compared to the age-matched normal subjects (Fig.1). IRI was high in all groups before the treatment (Table1). Following a 6-month treatment, FPG and HbA1c improved and IRI decreased in most patients (Table1). In parallel with the improvement of FPG and HbA1c, blood concentrations of DHEA and DHEA-S levels increased to within the normal range in all the groups (Fig.1).

	Number	FPG(mg/dl)	HbA1c(%)	IRI(μU/ml)
Male 40 years				
Before treatment	22	183±16	11.6±1.2	11.8±3.9
After treatment	22	111±14	7.2±0.6	8.7±2.1
Normal	20	93±7	5.2±0.3	5.9±2.3
Male 50 years				
Before treatment	29	172±18	11.7±1.2	12.4±3.7
After treatment	29	106±14	6.8±0.6	8.4±1.5
Normal	25	94±5	5.1±0.3	6.1±2.1
Male 60 years				
Before treatment	23	176±19	11.4±1.1	13.3±4.1
After treatment	23	108±14	6.7±0.6	8.9±3.4
Normal	20	90±7	5.2±0.2	5.8±1.8
Female 40 years				
Before treatment	17	172±16	12.0±1.1	11.9±3.2
After treatment	17	108±12	7.0±0.6	9.3±2.8
Normal	15	94±7	5.1±0.2	5.4±1.5
Female 50 years				
Before treatment	23	166±16	11.6±0.8	12.3±3.8
After treatment	23	112±15	7.1±0.4	8.1±2.4
Normal	20	92±7	5.1±0.3	4.8±1.6
Female 60 years				
Before treatment	16	175±19	11.9±1.2	11.6±2.8
After treatment	16	107±9	6.8±0.5	7.9±2.7
Normal	15	93±5	5.3±0.3	4.7±1.8

Table 1. Clinical characteristics of type 2 diabetic patients before and after treatment and in age-matched normal subjects.



*P< 0.05 compared with values after treatment and with normal values

Fig. 1. Serum DHEA and DHEA-S levels in male and female type 2 diabetic patients before (stippled bars) and after (hatched bars) treatment and in age-matched normal subjects (opena bars).

2.1.3 Discussion

In this study we demonstrated that serum DHEA and DHEA-S levels decreased markedly with poor control of type 2 DM and increased to age-matched normal values with the improvement of FPG and HbA1c after 6 months' treatment with diet and/or sulfonylurea. Barrett-Connor showed that DHEA and DHEA-S levels were also low in patients with non-insulin-dependent diabetes mellitus (Barrett-Connor, 1992), but she did not measure the changes of these steroid hormones after treatment. Markedly reduced levels of DHEA and DHEA-S in type 2 DM with poor therapeutic control with slightly increased plasma IRI are consistent with an association between DHEA synthesis and/or metabolism and insulin. Nestler et al. showed that insulin reduces serum DHEA and DHEA-S by increasing the metabolic clearance rate of DHEA in men or inhibiting their productin (Nestler,1992). The metablic clearance rate of DHEA is reported to be increased two- to fivefold in obesity and insulin-resistant, hyperinsulinemic state (Nestler,1995). The infusion of a high dose of insulin reduces serum DHEA levels suggesting the involvement of the inhibition of adrenal 17,20lyase activity. The administration of metformin which inhibits hepatic glucose production and enhances peripheral tissue sensitivity to insulin, to healthy normal weight men and to obese men with hypertension but without diabetes mellitus decreased serum insulin levels and increased serum DHEA-S levels in obese men with hypertension and in healthy controls (Nestler,1995). However, Yamauchi et al. reported that serum DHEA and DHEA-S are low even in patients with impaired glucose tolerance and low insulin response (Yamauchi,1996), and therefore the decrease in serum DHEA levels may not exclusively arise from the hyperinsulinemic state. Hyperglycemia may reduce 17,20-lyase activity and consequently serum DHEA may decrease. The improvement of plasma glucose control parallels the recovery of 17,20-lyase activity.

2.2 Basic study

The guinea pig utilizes a similar mechanism of adrenal steroidogenesis to that of humans. In a guinea pig model in which impaired glucose tolerance is induced by streptozotocin (STZ) treatment, we measured serum levels of DHEA, DHEA-S and c-peptide to determine if these were related to serum glucose levels.

2.2.1 Materials and methods

All experiments were performed using Hartley male guinea pigs with a body weight of 500-600 g. Experimental protocols followed the Principals of Laboratory Animal Care and were approved by the Ethics Committee of Toho University School of Medicine. Until experiments began, guinea pigs were housed in groups of three in metabolism cages in a temperature-controlled room with a 12h light/dark cycle. They had free access to tap water and guinea pig chow.

Under intra-abdominal anaesthesia (pentobarbital sodium 30mg/Kg), streptozotocin (STZ) was administrated to 12 guinea pigs intra-abdominally. After 4 weeks, a glucose tolerance test (50% glucose, 1g/Kg, intra-abdominal route) was performed. Impaired glucose tolerance (IGT) was defined as a blood glucose level of more than 300 mg/dl after 3 hrs. Six control guinea pigs had intra-abdominal saline only.

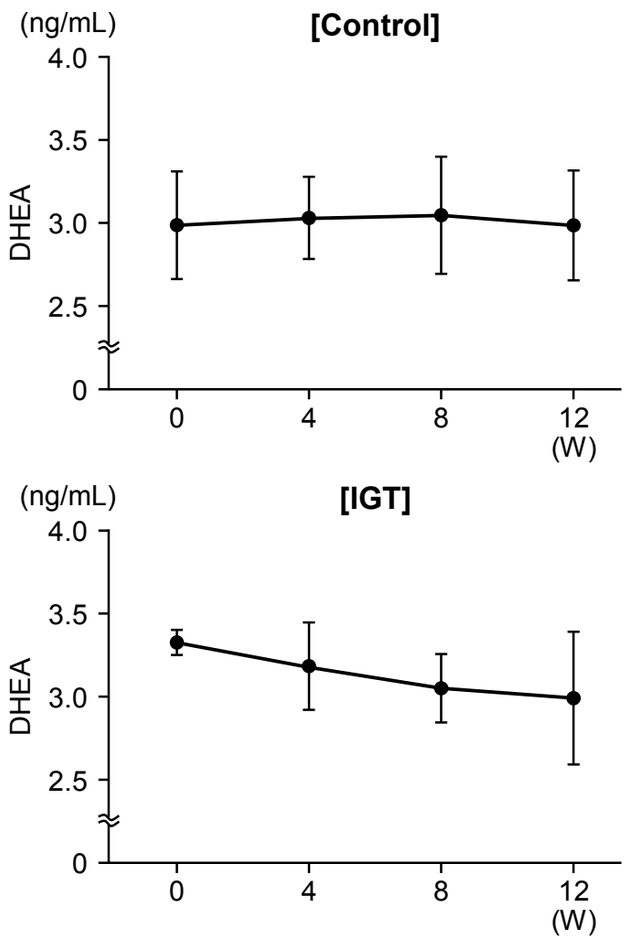


Fig. 2. Changes in Concentrations of Serum DHEA

Blood samples were taken from intra-orbital vessels after 12 hrs starvation. Serum DHEA, DHEA-S, fasting plasma glucose (FPG) and serum c-peptide were measured in each group at four time points: before STZ administration; after 4 weeks; after 8 weeks; and after 12 weeks. Simultaneously glucose tolerance tests were performed. From 15 weeks of STZ administration DHEA-S(Mylis) (20mg/Kg) was administrated via the intra-abdominal route three times per week in three IGT group guinea pigs and three control group animals. After 4 weeks, 8 weeks and 12 weeks of DHEA-S administration, blood samples were taken by the same method and glucose tolerance tests were also performed.
Data are expressed as mean±SD. Statistical analysis was performed using ANOVA with Bonferroni's correction. A value of $p<0.05$ was considered statistically significant.

2.2.2 Results

Concentrations of serum DHEA showed no significant change during observation in the control group, however there was a tendency towards decrease in the IGT group (Fig. 2). Concentrations of serum DHEA-S also had no significant change in the control group. However, in the IGT group, concentrations of serum DHEA-S decreased significantly from 39.0±4.2 μg/dl (before STZ administration) to 27.5±5.0 μg/dl (after 8 weeks)($p<0.05$)(Fig. 3).

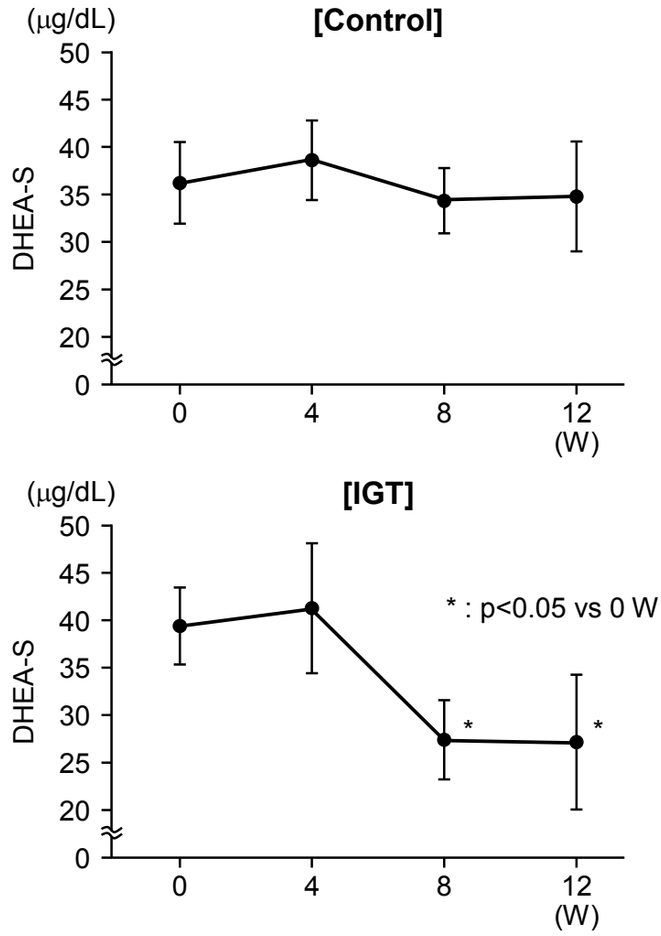


Fig. 3. Changes in Concentrations of Serum DHEA-S

Blood glucose levels three hours after DHEA-S administration showed no significant change between guinea pigs with DHEA-S and those without DHEA-S in the control group. In the IGT group, three hour blood glucose levels had improved from 333.7±24.5 mg/dl (before) to 190.7±89.8 mg/dl (after 4 weeks) (Fig. 4). However FPG showed no significant change between the control group and the IGT group. The result was similar after DHEA-S administration.

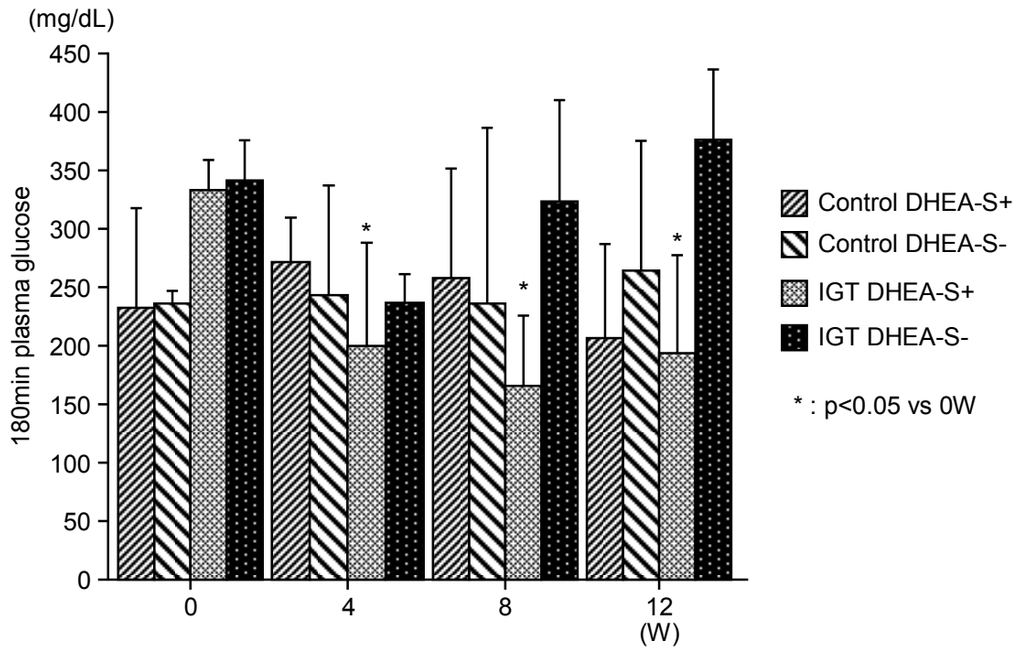


Fig. 4. Changes in 3 hour blood glucose level

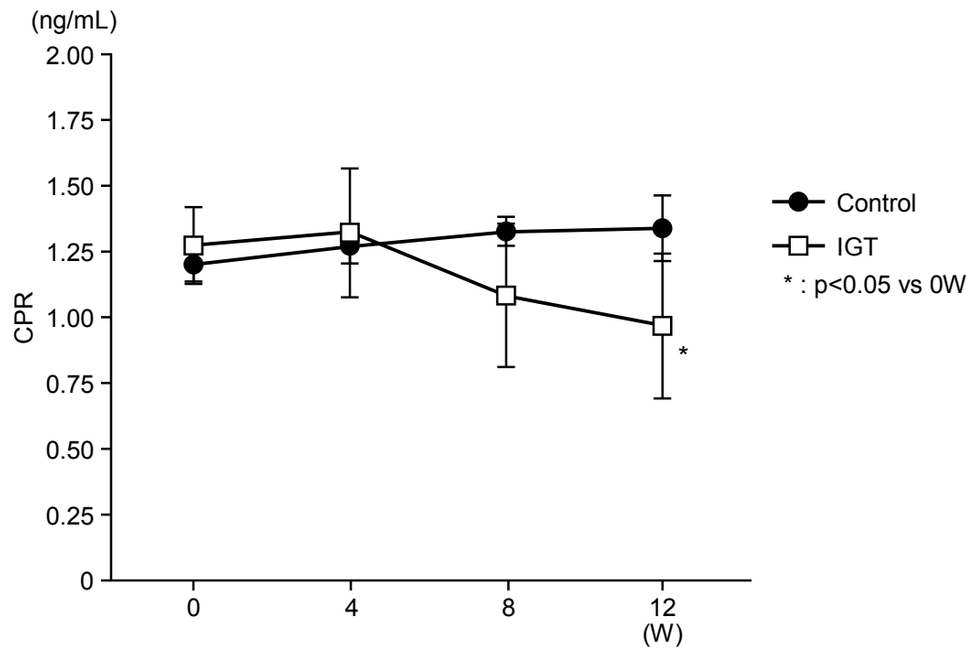


Fig. 5. Changes in serum C-peptide after STZ administration

Serum c-peptide levels showed no significant change during observation in the control group. However in the IGT group, these levels decreased significantly from 1.280±0.144 ng/ml (before) to 0.965±0.272 ng/ml (after 12 weeks)(Fig. 5). Serum c-peptide levels after DHEA-S administration were not significantly different between guinea pigs with DHEA-S and those without DHEA-S in both the control group and the IGT group. C-peptide levels continued to be significantly lower in the IGT group than in the control group (P<0.05) (Fig. 6).

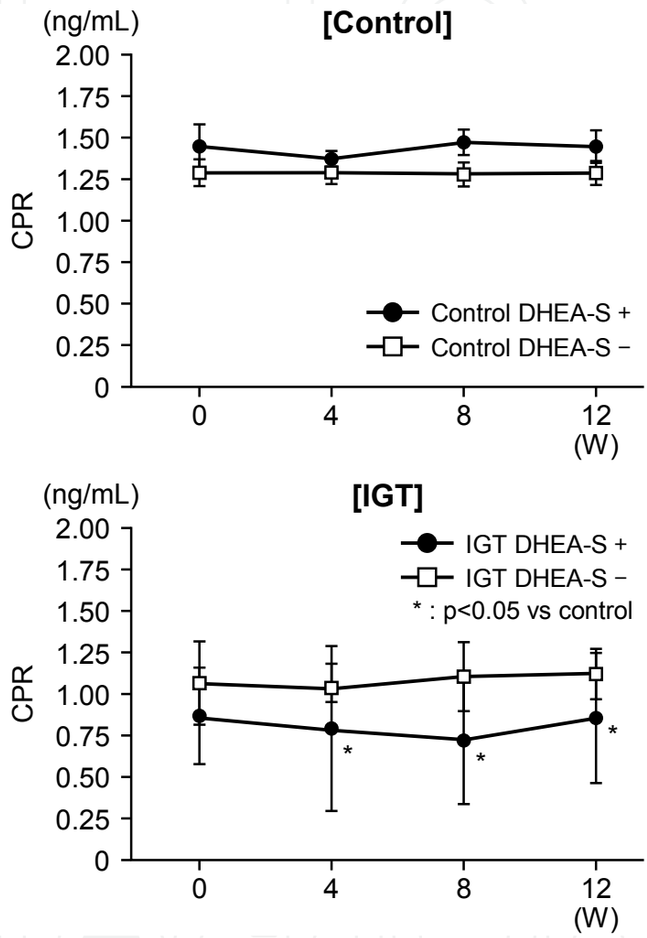


Fig. 6. Changes in serum c-peptide after DHEA-S administration

2.2.3 Discussion

Coleman et al.(1982). first reported that DHEA had an effect on lowering blood glucose in animal experiments. Since this report, there have been many reports that DHEA and DHEA-S are related to insulin or blood glucose levels. However, their exact role has not been determined (Gansler et al.,1985; Farah et al.,1992; Barrett-Connor,1992; Yamaguchi et al.,1998). Some of these reports described the use of rats and mice in animal experiments, but few studies used guinea pigs which have a similar mechanism of adrenal steroidogenesis to that of humans (Strott et al.,1981; Hyatt et al.,1983) In our guinea pig models in which impaired glucose tolerance is induced by STZ treatment , serum levels of DHEA and DHEA-S were decreased. We measured serum c-peptide instead of serum

insulin because there were no reports of serum insulin measurements in guinea pigs (Massey&Smyth,1975; Rosenzweig et al.,1980; Gracia-Webb et al.,1983; Schlosser et al.,1987). Guinea pigs in the IGT group showed a significant decrease in serum c-peptide levels and it was speculated that this was not hyper-insulinemia. In IGT group guinea pigs, blood glucose levels improved after DHEA-S administration, however serum c-peptide levels were still significantly decreased. There was no correlation between serum c-peptide levels and DHEA or DHEA-S levels. In the STZ-induced model of diabetes, adult rats ranged from mild type 2 diabetes to type 1 diabetes depending upon STZ dose (Ho RS et al.,1988). In this experiment, fasting blood glucose levels in STZ-administered guinea pigs were not significantly different from those in control group. However, serum c-peptide levels were decreased and this state was thought to be approaching type 1 diabetes.

Similar to clinical data, it was thought that hyperglycemia itself suppressed DHEA and DHEA-S after prolonged hyperglycemia independent of serum insulin levels in the absence of hyperinsulinemia. In IGT group guinea pigs, serum c-peptide was still decreased after DHEA-S administration, however blood glucose levels improved significantly. It was thought that DHEA-S itself was involved in this improvement of blood glucose levels. In the hyperglycemic state in humans, the mechanism of decrease of DHEA and DHEA-S levels is not still clear. It has been reported that DHEA levels are low in situations of life-threatening stress(Parker et al., 1985; Wade et al.,1988). Long duration hyperglycemia in this experiment is a form of excessive stress. It was speculated that histological changes in the adrenal gland may occur. The zona fasciculata which secretes cortisol necessary to maintain life may become enlarged and the zona reticularis which secretes DHEA and DHEA-S may shrink. In addition to reports of the mechanism of the improvement of impaired glucose tolerance by DHEA and DHEA-S, further studies reported a number of other effects. These included acceleration of glucose uptake in cells, increasing sensitivity in insulin sensitive tissue and suppressing the activities of G6Pase and FBPase, the enzymes of glyconeogenesis in the liver(McIntosh & Berdanier,1991; Nakashima et al.,1995) However, many points remained unclear.

3. Conclusion

These experiments suggest that the relationship between blood glucose levels and DHEA or DHEA-S is close. It is therefore possible that DHEA-S may become a therapeutic agent for diabetes mellitus in the future.

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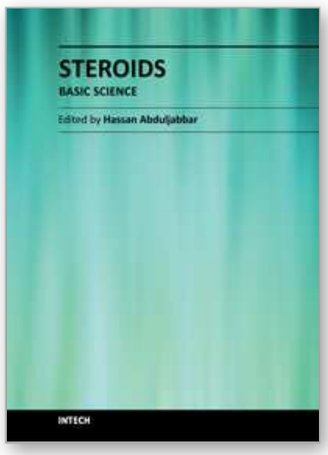

Steroids - Basic Science
Edited by Prof. Hassan Abduljabbar

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This book explains the basic science of steroids and is targeted towards professionals engaged in health services. It should be noted that medical science evolves rapidly and some information like the understanding of steroids and their therapeutic use may change with new concepts quickly. Steroids are either naturally occurring or synthetic fat-soluble organic compounds. They are found in plants, animals, and fungi. They mediate a very diverse set of biological responses. The most widespread steroid in the body is cholesterol, an essential component of cell membranes, and the starting point for the synthesis of other steroids. Since the science of steroids has an enormous scope, we decided to put the clinical aspects of steroids in a different book titled "Steroids-Clinical Aspects". The two books complete each other. We hope that the reader will gain valuable information from both books and enrich their knowledge about this fascinating topic.

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