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SHORT REPORT

Use of hormones in doping and cancer risk

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Abstract

Hormones with anabolic properties such as growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are commonly abused among professional and recreational athletes to enhance physical ability. Despite their adverse effects are well-documented, the use of GH and IGF-1 has recently grown. This article highlights the anabolic activity related to mechanisms of cancer development and progression. GH/IGF-1 axis is able to activate cellular mechanisms that modulate every key stage of cancer formation and progression, such as inhibition of apoptosis, resistance to treatments, and induction of angiogenesis, metastatic process and cell proliferation. Results from pre-clinical studies and epidemiological observations in patients with an excess of GH and IGF-1 production or treated with these hormones showed a positive association with the risk to develop several types of cancer. In conclusion, athletes should be made aware that long-term treatment with doping agents might increase the risk of developing cancer, especially if associated with other licit or illicit drugs and/or high-protein diet.

Introduction

Skeletal muscle is a plastic tissue, that responds to resistance training or amino acid ingestion, by altering protein synthesis and degradation in favor of tissue growth, or anabolism. These responses could be induced by hormones with anabolic properties, able to increase protein synthesis and/or decreasing protein degradation through a variety of downstream pathways after binding their respective receptors (1).

The enhancements of muscle mass and/or performance induced by supplementation with anabolic androgenic steroids (AAS) such a testosterone and its natural or synthetic analogues, have encouraged athletes to use them as performance enhancing drugs for a competitive edge.

Along with AAS, increased muscle anabolism can be illicitly attained with different peptide hormones such as chorionic gonadotropin, luteinizing hormone, the growth hormone (GH) and the insulin-like

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growth factor (IGF-1). Despite the use of testosterone and its derivatives has been described extensively, less attention has been placed on the use of other non-androgenic anabolic agents (NAA) such as GH and IGF-I.

GH promotes bodily development by increasing the length of the bones and muscle mass and reducing adipose tissue. IGF-1 acts in synergy with the GH by promoting anabolism, reducing body fat and providing energy by stimulating the entry of glucose into cells. However, the extent to which GH can have an anabolic effect and the potential mechanisms mediating such effects at physiologic doses remains controversial.

This article focuses on the need to pay more attention to the long-term risk of NAA use associated with cancer development, given the strong physiological/molecular relation between IGF-1/GH axis and cancer.

Use of AAS and NAA as performance enhancing drugs

Anabolic steroids are often taken by athletes orally or intramuscularly using an "accumulation" regime to enhance the anabolic effects, minimize side/adverse effects and reduce the risks of positive responses to doping controls: all this involves alternate intakes through the oral and intramuscular routes for several weeks before a sports competition. Regardless of sports ethics, it is difficult to scientifically face the problem of the real effectiveness of the use of AAS in sport. The analysis of the literature does not help to solve the questions about their real utility in inducing a training-dependent increase in muscle masses and, even more, if this increase is responsible for an improvement in performance. This uncertainty depends on the methodological lack of research (few cases, superficial statistical analysis, inhomogeneity of test conditions) and on the variety of effects sought (morphological or performance analyzes). Several studies were able to demonstrate a significant increase in body mass, weight and strength in weight lifters who continued to train during anabolic steroid treatment (2).

Currently, AAS are used by millions of men, and numerous clinical studies suggest that about 30% of those who use AAS illegally develop an addiction. Regarding NAA, GH is used by bodybuilders because it is considered very valuable for maximizing the sculptural appearance of the muscles.

IGF-1 is assumed by some athletes in the belief that it can have anabolic effects enhancing the action of GH. However, the IGF-1 liver secretion is stimulated by GH, and there is currently no direct *in vivo* human evidence to suggest that IGF-1 significantly increases muscle mass (1).

The typical user is a male, athlete, usually a football player, a heavyweight wrestler or a weightlifter (3). The prevalence of AAS use is comprised in a range from 4-6 % and 1.5-3 % for adolescent male and female athletes, respectively (4), to 20-50 % in adult bodybuilders. However, other scientific evidence showed that the use of AAS is a major problem for general population instead of athletes, because associated with other problematics such as drug use (2).

Adverse effects of NAA

The adverse effects related to GH abuse in humans, are believed to be similar to those observed in acromegaly which may result in hypertension, carpal tunnel syndrome, diabetes, and neuropathy among many others. In addition, other pathological conditions such as edema, arthropathy and gynecomastia may occur. Most features of IGF-1 misuse will not be distinguishable from those that develop from GH abuse, since IGF-1 production is

mainly promoted by increased GH levels. However, hypoglycemia, seizures, jaw pain, myalgia, edema, headaches, increased liver and kidney mass, and altered liver function have been reported after recombinant human IGF-1 (rhIGF-1) administration (1).

Correlations between GH/IGF-1 axis and cancer

In recent years, GH and IGF-1 have been strongly related to the capacity to influence cell growth and have been suggested to be involved in cancer development and progression. In particular, several epidemiological data showed that elevated serum levels of GH and IGF-1 and the upregulation of their pathways seem to modulate every key stage of cancer formation and progression; the main mechanisms involved comprise the inhibition of apoptosis, resistance to treatments, induction of angiogenesis and metastatic process, resulting in an increased risk of different common cancer types, such as breast, colorectal, lung and prostate cancer (5-9). IGF-1 activates the intracellular signaling pathways binding to its tyrosine kinase receptor (IGF-1R) that phosphorylates the insulin-receptor substrate-1, which in turn activates phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR and Ras/Raf/mitogen activated protein kinase (MAPK) pathways (5). The IGF-1 receptor (IGF-1R) activation and its intracellular cascade are crucial in transformation and survival of tumour cells while it is only partially required for normal cell growth. This receptor is ubiquitously expressed in normal tissues and in a wide range of haematologic neoplasias or solid tumours, such as prostate, breast and colon cancer. The activation of IGF-1R modulates the apoptotic process, leading to an upregulation of caspase-inhibitors or Bcl-2 family members, increasing the survival rates of cells and their exposition to genetic hits. Furthermore, throughout IGF-1R activation, IGF-1 and IGF-1 isoforms trigger transcriptional regulators involved in cell survival, resistance to treatments and telomerases elongation, leading to increased and unlimited proliferative potential of cancer cells (10, 11). GH/IGF-1 axis is involved also in the angiogenetic mechanism, increasing the expression of the vascular endothelial growth factor (VEGF); evidence suggested that this process is mediated by the MAP kinases signaling in colon cancer cells (12). It has been also confirmed that IGF-1 is involved in VEGF overexpression by *in vivo* experiment, administrating IGF-1 in mice (13).

Clinical studies

In the AAS users, the increase in bilirubin, alkaline phosphatase and transaminases are the main biochemical changes detectable in the blood. The prolongation of the administration can cause the appearance of hepatic peliosis, a pretumor alteration characterized by blood microcysts, the rupture of which can induce severe bleeding and morphofunctional disorders. Tumor forms show higher incidence in young or young adult subjects and histologically appear as hepatocellular carcinomas. Overall, the risk of the onset of severe liver changes must always be taken into due consideration, even if there is no adequate epidemiological investigation related to healthy subjects who, due to doping, have made prolonged use of AAS (2). A number of epidemiological studies examined the possible link between cancer and increased levels of GH/IGF-1. An increased frequency of colon carcinoma among patients affected by acromegaly with high IGF-1 levels suggests a role of GH/IGF-1 in cancer development (14). Moreover, it was observed that women with breast cancer had elevated serum GH levels (15) and patients with breast and prostate cancer

had increased circulating IGF-1 levels (16). Moreover, several data suggested that it cannot be excluded that diet composition, high consumption of amino acids and high-protein diet needed to increase muscle mass, could further amplify the potential cancer risk associated to the treatment with GH/IGF-1 (17). Some studies reported the increased risk of colorectal cancer and Hodgkin lymphoma in patients treated with GH for growth during their childhood or as replacement treatment in adults (18, 19). However, these finding were not confirmed by other studies, and the current international surveillance data do not support the increase of malignancies after recombinant GH or IGF-1 treatment.

Conclusions

In conclusion, strong experimental *in vitro* evidences as well as *in vivo* pre-clinical studies support the potential role of GH and IGF-1 in cancer from a mechanistic point of view. Even more, worrying is the fact that also epidemiological studies show a positive correlation between GH and IGF-1 levels and cancer risk. Furthermore, cancer risk associated to doping might be higher than that of patients using hormones/growth factors as replacement therapy: indeed, as compared to these established treatments, athletes take enormous doses for long time periods (20, 21). In addition, these substances are often used in combination with other licit or illicit drugs and this makes difficult to quantify the possible adverse effects including cancer. Anyway, athletes should be made aware that long-term treatment with doping agents might increase the risk of developing cancer, and secondary prevention strategies in AAS user are needed.

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Additional documents and the Italian version is available at: www.sitinazionale.it/BDS/muoversi and/or at link www.progettodoping.it

Riassunto

Utilizzo di ormoni nel doping e rischio di cancro

Ormoni con proprietà anaboliche come l'ormone della crescita (GH) e il fattore di crescita insulino-simile-1 (IGF-1) sono comunemente usati sia da atleti professionisti che amatoriali, per migliorare le capacità fisiche. Nonostante i loro effetti collaterali siano ben documentati, l'uso di GH e IGF-1 è recentemente cresciuto. Questo articolo evidenzia come l'attività anabolica sia legata ai meccanismi di sviluppo e progressione del cancro.

L'attività sinergica di GH e IGF-1 è in grado di attivare meccanismi cellulari che modulano ogni stadio chiave della formazione e della progressione del cancro, come inibizione dell'apoptosi, resistenza ai trattamenti, e induzione di angiogenesi, processi metastatici e proliferazione cellulare. I risultati di studi preclinici e osservazioni epidemiologiche in pazienti con eccessiva produzione di GH e IGF-1 o trattati con questi ormoni hanno mostrato un'associazione positiva con il rischio di sviluppare diversi tipi di cancro. In conclusione, gli atleti dovrebbero essere ben consapevoli che il trattamento a lungo termine con agenti dopanti può aumentare il rischio di sviluppare il cancro, specialmente se associato ad altre droghe lecite o illecite e/o dieta iperproteica.

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