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Use of Growth Hormone, IGF-I, and Insulin for Anabolic Purpose: Pharmacological Basis, Methods of Detection, and Adverse Effects

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Abstract

Hormones with anabolic properties such as growth hormone (GH), insulin-like growth factor-1 (IGF-I), and insulin are commonly abused among professional and recreational athletes to enhance physical ability. Performance enhancing drugs (PEDs) such as these are also commonly used by recreational athletes to improve body aesthetics. The perception of increased muscle mass due to supraphysiologic hormone supplementation, or doping, is widespread among PED users despite a paucity of evidence-based data in humans. Even still, athletes will continue to abuse PEDs in hopes of replicating anecdotal results. It is important to educate the general public and potential treating physicians of the risks of PED use, including the dangers of polypharmacy and substance dependence. It will also be important for the research community to address the common challenges associated with studying PED use such as the ethical considerations of PED administration, the general reticence of the PED-using community to volunteer information, and the constant need to improve or create new detection methods as athletes continually attempt to circumvent current methods. This review highlights the anabolic mechanisms and suggestive data implicating GH, IGF-I, and insulin for use as PEDs, the specific detection methods with cutoff ranges that may be utilized to diagnose abuse of each substance, and their respective side effects.

Keywords

drug abuse; performance enhancing drugs; muscle; side effects; doping; sports

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Introduction

Skeletal muscle is critical for execution of movement, thermogenesis, and nutrient metabolism. Proficiency of these processes is dependent on skeletal muscle mass which is largely regulated by exercise, nutrition, hormones, and to a lesser extent, genetics and ethnicity. As skeletal muscle is a plastic tissue, it responds to progressive overload, such as resistance training, or amino acid ingestion by altering protein synthesis and degradation in favor of tissue growth, or anabolism. Hormones with anabolic properties induce similar responses in skeletal muscle, increasing protein synthesis and/or decreasing protein degradation through a variety of downstream pathways after binding their respective receptors.

Reported enhancements of muscle mass and/or performance from supplementation with exogenous anabolic hormones have encouraged athletes to seek out performance enhancing drugs (PED) for a competitive edge. In an effort to protect elite and professional athletes from the unknown health consequences of PED abuse, the 2004 Anabolic Steroid Control Act expanded the list of controlled substances regulated by the federal government to include naturally occurring precursors of testosterone, growth hormone (GH), and insulin-like growth factor 1 (IGF-I). Although efforts have been made to protect athletes from doping, PED use has also spread to non-professional athletes and to the general population due to ease of access via the web and black market. These individuals have turned to PEDs primarily to improve body aesthetics (Pope, Khalsa and Bhasin, 2017) but also to improve energy levels, sex drive, and athletic performance (Creado and Reardon, 2016).

The use of anabolic-androgenic steroids (AAS) such as testosterone and its derivatives has been described extensively (Creado and Reardon, 2016, Pope, Wood, Rogol et al., 2014); however, less attention has been placed on the use of other common PEDs such as GH, IGF-I, and insulin. In 1992, 5% of male high school students admitted to taking GH at some point in their high school sport careers, and about one-third of the participants knew a classmate who had taken GH (Rickert, Pawlakmorello, Sheppard et al., 1992). Middle-aged and elderly people often seek GH with hopes of improving muscle mass and obtaining more youthful physical qualities. PED abuse has also grown in the weightlifting community with 27 of 231 (12%) weightlifters polled reporting past and/or present GH or IGF-I use with over 80% of those polled also exhibiting signs of past or present AAS dependency (Brennan, Kanayama, Hudson et al., 2011). Insulin is also a commonly used PED by body builders for its purported anabolic properties such as stimulation of glycogen formation, which is important for muscle recovery after exercise, and its accessibility from local pharmacies (Dawson and Harrison, 1997, Evans and Lynch, 2003).

At the molecular level, the balance of anabolic and catabolic (protein degrading) processes is coordinated primarily by the phosphoinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR)/Forkhead boxO3a (FOXO3a) pathway among others (Glass, 2005). mTOR is a key mediator contributing to muscle protein synthesis and can be activated by PI3K/Akt (Gulati, Gaspers, Dann et al., 2008), which are, in turn, activated by growth factor signaling, such as insulin and IGF-I (Sandri, 2008). Akt phosphorylates, thereby inhibiting, FOXO3a which is a transcription factor that induces the proteosomal pathway by up-

regulating the ubiquitin ligases atrogin-1 and muscle RING finger 1 (MuRF-1) (Salih and Brunet, 2008, Stitt, Drujan, Clarke et al., 2004). Akt also inhibits glycogen synthase kinase 3 (GSK3), removing the GSK3-induced inhibition of mRNA translation initiation (Leger, Cartoni, Praz et al., 2006). Importantly, when the size of a muscle fiber increases, activation of muscle precursor cells, or satellite cells, is required for provision of additional nuclear machinery to support the growing tissue (Hawke and Garry, 2001). Activation of Akt also affects glucose metabolism inducing an increase in glucose and amino acid uptake (Edinger and Thompson, 2002, Kohn, Summers, Birnbaum et al., 1996). Growth hormone, IGF-I, and insulin are known to influence these pathways, which have provided the basis for their use as PEDs (see figure 1).

This review will highlight the pharmacologic basis for and misuse, detection, and side effects of GH, IGF-I, and insulin as PED in sports and the larger recreational community. The impact of polypharmacy will also be addressed as this is an important factor in doping regimens.

Anabolic potential of GH, IGF-I, and Insulin use

Growth Hormone

The extent to which GH itself induces significant anabolism is still a matter of debate. Growth hormone's anabolic effects in muscle are mediated in part via IGF-I (Kim, Barton, Muja et al., 2005), although IGF-I-independent pathways have also been proposed (Daughaday, 1989, Isaksson, Lindahl, Nilsson et al., 1988, Le Roith, Bondy, Yakar et al., 2001, Sotiropoulos, Ohanna, Kedzia et al., 2006). IGF-I is made in the liver but also in other tissues including skeletal muscle which express the GH receptor (Jorgensen, Jessen, Pedersen et al., 2006, Mathews, Norstedt and Palmiter, 1986). The interplay between circulating IGF-I and IGF-I locally produced in muscle is not fully understood but it is likely that both forms play a role in muscle growth. After administration of recombinant human (rh)GH in combination with resistance exercise, GH release after exercise was associated with increased expression of muscle-specific IGF-I (MGF) (Hameed, Lange, Andersen et al., 2004) which activates satellite cells for fusion with muscle fibers (Hill and Goldspink, 2003).

Adult GH deficiency (AGHD) is characterized by a decrease in muscle mass and strength along with increased adiposity (Jorgensen et al., 2006, Cuneo, Salomon, Wiles et al., 1990, Hoffman, Osullivan, Freund et al., 1995). Exercise capacity is also decreased and these patients often complain of fatigue being one of the main contributors to reduced quality of life. GH replacement using physiologic doses of 0.2–1.0 mg/day (estimated range for an 80 kg person based on various units used to report dosing regimens among studies) in this setting is associated with improvements in body composition (increases in lean mass and decreases in fat mass) in some studies (Bengtsson, Eden, Lonn et al., 1993, Salomon, Cuneo, Hesp et al., 1989, Snel, Brummer, Doerga et al., 1995, Lonn, Johansson, Sjostrom et al., 1996, Jorgensen, Thuesen, Muller et al., 1994, Woodhouse, Asa, Thomas et al., 1999, Blackman, Sorkin, Munzer et al., 2002), although other reports looking directly at muscle cross sectional area showed no changes over a 6-month period (Cuneo, Salomon, Mcgauley et al., 1992). GH [0.5–2.2 mg/day] has been shown to increase exercise capacity and

improve fatigue scores and overall quality of life in this population (Gilchrist, Murray and Shalet, 2002, Widdowson and Gibney, 2008, Rubeck, Bertelsen, Vestergaard et al., 2009). Also, GH has been shown to increase muscle mass and strength after 3 years (Jorgensen et al., 1994) and after 10–15 years (Elbornsson, Gotherstrom, Bosaeus et al., 2013, Gotherstrom, Elbornsson, Stibrant-Sunnerhagen et al., 2009) although no effect was detected on fiber type with 6 months of treatment on a different report (Cuneo, Salomon, Wiles et al., 1992). In addition, two meta-analyses reported no effect on muscle strength after less than 12 months of treatment (Rubeck et al., 2009, Widdowson and Gibney, 2010). Regarding its effects at the molecular level, GH does not affect protein degradation directly but it appears to enhance protein synthesis in skeletal muscle via IGF-I-dependent mechanisms (Le Roith et al., 2001). Nevertheless, other studies have failed to see an effect of GH at the muscle level (Copeland and Nair, 1994, Yarasheski, Zachwieja, Angelopoulos et al., 1993). In summary, the extent to which GH can have an anabolic effect and the potential mechanisms mediating such effects at physiologic doses remain controversial.

Insulin-like growth factor-1

IGF-I receptor activation promotes muscle anabolism by activating PI3K/Akt (Velloso, 2008). In addition to these anabolic effects, IGF-I-induced activation of PI3K/Akt is also the reported mechanism by which IGF-I inhibits mitochondrial apoptosis (Pang, Zheng, Fan et al., 2007). Other effects on transcription have also been described via activation of mitogen activated protein kinases (MAPKs) (Leinninger, Backus, Sastry et al., 2005, Palacios, Sanchez-Franco, Fernandez et al., 2005, Song, Li, Du et al., 2005) which relay hypertrophic signals to myonuclei after contraction; however, explicit mechanisms are not well characterized (Martineau and Gardiner, 2001). IGF-I also promotes glycogen synthesis (Park, Kido and Accili, 1999), tendon collagen synthesis (Abrahamsson and Lohmander, 1996) and may indirectly promote GH-induced lipolysis (Vikman, Isgaard and Eden, 1991). Given the similarities between the IGF-I receptor and the insulin receptor, there is some cross-reactivity that accounts for similar side effects such as hypoglycemia (Ullrich, Gray, Tam et al., 1986). IGF-I has also been shown to induce proliferation and differentiation of satellite cells into myocytes (Musaro, McCullagh, Naya et al., 1999). Administration of IGF-I down-regulates proteolysis but does not appear to alter protein synthesis (Hussain, Schmitz, Mengel et al., 1994). This data is in contrast with the effects of GH on protein metabolism described above and suggest that these actions of GH are IGF-I independent and complimentary.

Insulin

The anabolic potential of insulin has been recognized since it was first used for the treatment of diabetes (Cefalu, 2004, Peterson, 1982). Insulin exerts these anabolic effects by increasing the transport of glucose and amino acids into skeletal muscle fibers, thereby increasing protein synthesis and decreasing protein degradation (Biolo, Fleming and Wolfe, 1995). Insulin binds to its receptor, causing phosphorylation of insulin receptor substrate (IRS) proteins, which in turn, activates the PI3K/Akt pathway. This process may be enhanced by administering insulin after a bout of exercise since this is known to increase insulin sensitivity in muscle for up to 24–48 h (Dawson and Harrison, 1997). Insulin may also promote muscle anabolism indirectly by increasing appetite via its hypoglycemic

effects (Sprague, 2011), and by inhibiting fatty acid oxidation in muscle (Sidossis, Stuart, Shulman et al., 1996). In contrast, insulin may act centrally to reduce appetite and increase energy expenditure long term (Dallman, Akana, Strack et al., 1995, Ikeda, West, Pustek et al., 1986). As most reports of insulin-induced anabolism are anecdotal, there are no in-vivo reports in humans studying its anabolic potential. Insulin also induces lipogenesis leading to an increase in fat mass and body weight. This may be undesirable for certain activities where leanness is sought.

GH, IGF-I and insulin used as PED

Growth Hormone

The emergence of GH as a PED began sometime before 1985 when the first description of its purported effects and recommendations for performance enhancement was published (Duchaine, 1982). Shortly thereafter, Ben Johnson, who won the 100m gold medal in the Seoul Olympics in 1988, was stripped of his medal after admitting under oath to using GH and anabolic steroids. GH was banned by the International Olympic Committee in 1989 and "off-label" distribution/prescription was declared felonious by Congress with the Crime Control Act of 1990. Various scandals and reports have surfaced over the ensuing years which continue to highlight the prevalence of GH usage by professional athletes (Holt and Sonksen, 2008). Despite being one of the most widely abused agents both professionally and recreationally (Holt and Sonksen, 2008, Barroso, Mazzoni and Rabin, 2008, Chikani and Ho, 2014), there is little clinical evidence that GH in isolation has any significant effect on performance enhancement.

Aerobic exercise capacity is not affected by GH at physiologic doses in healthy individuals (reviewed here (Chikani and Ho, 2014)) or in AGHD patients (Chikani, Cuneo, Hickman et al., 2016). However, physiologic doses may improve anaerobic capacity in AGHD patients (Chikani and Ho, 2014, Chikani et al., 2016). A study using supraphysiologic doses of GH [2mg/day] in recreational athletes showed no effect on muscle strength or VO^2 max although it did improve anaerobic capacity (Meinhardt, Nelson, Hansen et al., 2010). A different study using the same dose showed increases in lipid oxidation and lipolysis which contribute to a decrease in adiposity and may make more nutrients available to muscle (Krag, Gormsen, Guo et al., 2007). It is also important to note that states of GH-excess, such as acromegaly, are associated with muscle weakness and fatigue (Flitsch, Spitzner and Ludecke, 2000), suggesting that chronically elevated levels of GH or IGF-I have a deleterious effect on muscle. GH [0.2–2 mg/day] has also been tested in conjunction with exercise for up to 6 months and was found to be similar to exercise alone (Hennessey, Chromiak, DellaVentura et al., 2001, Lange, Andersen, Beyer et al., 2002, Yarasheski, Campbell, Smith et al., 1992, Yarasheski, Zachwieja, Campbell et al., 1995). Despite these data, it should be noted that hypopituitarism remains the only indication for GH administration in adults (Clemmons, Molitch, Hoffman et al., 2014).

GH's popularity remains evident through its increased affordability and online availability to consumers (Brennan et al., 2011). From a poll of 231 male weightlifters from the United States, 100 admitted past and/or present PED use of any kind, and 26 admitted past and/or present GH use (Brennan et al., 2011). Its prevalence was reported to be just below 10%

among recreational and professional bodybuilders in Iran and was 34% (GH or GH-releasing peptide) among recreational weightlifters in the UK (Haerinejad, 2016, Chandler, 2014). GH is administered subcutaneously at doses of 0.2–1.0 mg/day for AGHD based on an 80 kg person (Carroll, Christ and Comm, 1998). The dosage for improving muscle mass, typically for bodybuilders, is reported in the range of 3–8 mg/day, three to four times a week in cycles of four to six weeks (Saugy, Robinson, Saudan et al., 2006). Relatively little is known about the typical GH regimen used by endurance athletes.

IGF-I

IGF-I is typically used to enhance the anabolic effects of concurrent GH and/or anabolic steroid use. It has been on the World Anti-Doping Association's prohibited list since the World Anti-Doping Code was established in 2003. Prevalence of its use as a PED was reported to be 16% of patients admitted to a Swedish addiction clinic, over 6% (including IGF-I and MGF) in a UK survey disseminated to online weightlifting forums to participants of needle exchange programs, and 7% in a poll of weightlifters from the United States (Brennan et al., 2011, Chandler, 2014, Skarberg, Nyberg and Engstrom, 2009). The lower incidence of IGF-I use, in comparison to GH use, is partly attributed to the difficulty in drug preparation and accessibility. However, there have been many accounts of its availability on the black market (Holt and Sonksen, 2008, Baumann, 2012, Guha, Cowan, Sonksen et al., 2013). IGF-I is only approved for treatment of patients with primary severe IGF-I deficiency or with GH gene deletion that have developed neutralizing antibodies to GH at a dose of 40–120 μg/kg twice daily subcutaneously. When administered to patients with Type 2 Diabetes at doses of 200–240 μg/kg/day, it significantly reduced blood glucose levels (Moses, Young, Morrow et al., 1996, Zenobi, Jaeggigroisman, Riesen et al., 1992). Consequently, IGF-I is administered with a meal to avoid hypoglycemia.

The typical regimen of IGF-I use among the American weightlifters was 50–75 μg/day with median lifetime duration of 9 weeks (Brennan et al., 2011). This dose appears particularly low in comparison to those used in Type 2 Diabetes; however, the authors were fairly skeptical of the accuracy of these doses reported. Marked anabolism occurred in mice over-expressing IGF-I (Coleman, Demayo, Yin et al., 1995) and IGF-I administration (30–60 μg/kg twice a day, ~3600–8600 μg/day based on reported mean body weight) improved whole body and muscle protein synthesis in elderly women (Butterfield, Thompson, Rennie et al., 1997). However, there is currently no direct in vivo human evidence to suggest IGF-I significantly increases muscle mass. One year of IGF-I treatment (15 μg/kg bid, ~2200 μg/day based on reported mean body weight) failed to improve muscle mass in postmenopausal women (Friedlander, Butterfield, Moynihan et al., 2001).

Insulin

Although there is a paucity of data on the use of insulin as a PED, it appears to be commonly abused because it is inexpensive and readily available in most settings. Its prevalence was reported to be just below 10% among recreational and professional bodybuilders in Iran (Haerinejad, 2016) and among recreational weightlifters in the UK (Chandler, 2014) and 25% among a small group of recreational bodybuilders in the US (Rich, 1998). The International Olympic Committee banned its use in 1998 for those without

diabetes (“International Olympic Committee and Medical Commission,”) but its use also appears to be increasing among recreational weight lifters. Insulin is usually obtained from local sources (e.g., friends, training partners, gym member/dealer) or from community pharmacies where it is available without a prescription (Evans and Lynch, 2003, Elkin, Brady and Williams, 1997). It is usually administered right before a post-workout meal or along with glucose or with amino acids with the purpose of preventing hypoglycemia while shutting off proteolysis and increasing protein synthesis (Evans and Lynch, 2003). Short acting insulin or insulin analogs (regular, lispro, aspart, etc.) appear to be the most common forms of insulin used once a day subcutaneously or intramuscularly in the range of 2–15 IU/dose (Dawson and Harrison, 1997). Among the group of weightlifters polled in the US, a mean of 10 IU per injection was reported with users obtaining dosing information by word of mouth (Rich, 1998). Insulin administration (1.5 μU/kg/min, mean 45 days) after severe burn significantly increased total, trunk, and peripheral lean mass (Thomas, Morimoto, Herndon et al., 2002); however, there is no evidence of improved muscle mass after insulin administration in healthy adults at this time.

Methods of Detection

Growth Hormone

Unlike anabolic steroids which can be detected by mass spectroscopy from urine samples, GH is measured by immunoassay from blood samples because of low and variable GH excretion levels. However, due to the pulsatile release of GH, detection of elevated GH levels may simply reflect peak circulating levels and not necessarily indicate exogenous GH use. In addition, recombinant human GH is virtually indistinguishable from the endogenous 22-KDa form, including having a very short half-life, with levels returning to normal 8–20 hours after administration (Barroso et al., 2008). Consequently, an isoform differential immunoassay method, also considered the “direct” method, was derived to detect exogenous GH use (Bidlingmaier, Wu and Strasburger, 2000, Wu, Bidlingmaier, Dall et al., 1999). Under normal conditions, circulating GH levels occur as a mixture of different isoforms in specific proportions. Between 75–80% of circulating GH is the 22-KDa isoform, 5–10% is the 20-KDa isoform, and the remaining levels occur as dimers, oligomers, and various other isoforms (Baumann, 2012). In contrast, rhGH levels only occur in the 22-KDa form. Endogenous GH is suppressed after administration of rhGH, thereby increasing total 22-KDa levels and levels relative to the other isoforms for up to 4 days (Wallace, Cuneo, Bidlingmaier et al., 2001). One differential immunoassay recognizes only the 22-KDa isoform while the other recognizes a combination of isoforms. As a result, the ratio of the two detection levels can be used to determine if rhGH was administered within 36 hours but it is recommended that sampling time should be less than 24 hours for increased accuracy (Pope et al., 2014, Baumann, 2012). The ratio of 22-KDa-only levels to level of multiple isoforms has a median value of 0.8. The ratio limits for determination of rhGH abuse by the World Anti-Doping Agency range from 1.68–1.81 for men and 1.46–1.55 for women (“2010 World Anti-Doping Agency Guidelines: hGH isoform differential immunoassays for anti-doping analyses, version 1.0, June 2010.,”).

Alternatively, there is an “indirect” or “biomarker” method of detecting rhGH abuse which examines the downstream biomarkers of GH activity. The predominantly tested biomarkers are IGF-I and procollagen type III amino-terminal propeptide (P-III-NP) due to their particular responsiveness to GH. Circulating IGF-I, measured my immunoassay or liquid mass spectroscopy, rises rapidly within 2 weeks after rhGH use and then falls to baseline levels within 1 week after rhGH cessation. Levels of P-III-P, measured by immunoassay, increase gradually within 4–6 weeks of rhGH initiation then return to normal after 2–8 weeks (Pope et al., 2014, Baumann, 2012, Dall, Longobardi, Ehrnborg et al., 2000). The results of these two assays are incorporated into a formula taking into account age and gender (Powrie, Bassett, Rosen et al., 2007) to differentiate between those using or not using rhGH when carried out within 7 days of rhGH administration, which is a much longer window of opportunity than the direct method (Pope et al., 2014). Other biomarkers explored, but ultimately not determined suitable, for this method were the liver factors IGF binding protein (IGFBP)-2, IGFBP-3, and acid-labile subunit (ALS), and bone turnover markers procollagen type I carboxyl-terminal propeptide and type 1 collagen cross-linked carboxy-terminal telopeptide (Barroso et al., 2008). Detection by using the biomarker method may highlight disruption of the GH/IGF-I axis for various exogenous GH-related agents (i.e. rhGH, GH-releasing hormone analogs, GH secretagogues, etc.).

Insulin-like growth factor-1

While there is no current standard method for determination of IGF-I abuse, detection of IGF-I is typically accomplished by immunometric, noncompetitive assays because of increased specificity and speed of completion. However, these assays do require acid-ethanol precipitation or addition of excess IGF-2 to minimize binding protein interference (Guha et al., 2013). Current investigations of detection methods for IGF-I abuse in athletes are formulated to also detect IGFBP-3 abuse and are based on the same principle as the biomarker method for determination of GH abuse. Markers of IGF-I/IGFBP-3 administration include increased IGF-I and IGFBP-2, decreased P-III-NP and IGF-2, and decreased ALS in women (Guha et al., 2013, Guha, Erotokritou-Mulligan, Bartlett et al., 2014, Holt, 2017).

Insulin

Assays for measurements of insulin are readily available given their use in the evaluation of hypoglycemia. When insulin abuse is suspected, evaluation should be performed when the patient is hypoglycemic, which may be challenging in this population unless they seek medical care during such an episode. A plasma insulin concentration of 3 IU/mL (20.8 pmol/L) or more by immunochemiluminometric assay (ICMA) when the plasma glucose concentration is below 55 mg/dL (3.0 mmol/L) suggests inappropriate hyperinsulinemia. Measurements of plasma C-peptide and proinsulin levels will help distinguish endogenous from exogenous hyperinsulinemia. C-peptide <200 pmol/L (0.6 ng/mL) and proinsulin <5pmol/L when glucose is <45 mg/dL and elevated insulin levels suggest exogenous insulin use. With the development of insulin analogs, one important caveat is that insulin concentrations may be falsely low depending on the cross-reactivity with the particular assay used. Specific assays now detect a variety of insulins including human insulin, animal insulin, and insulin analogs (Andersen, Jorgensen, Jensen et al., 2000, Bowsher, Lynch,

Brown-Augsburger et al., 1999, Moriyama, Hayashi, Ohyabu et al., 2006, Neal, 2008, Walfish, Feig and Bauman, 1987). Urinary liquid chromatography/tandem mass spectroscopy has also been proposed to detect insulin analogs (Holt and Sonksen, 2008).

Adverse Effects

Growth Hormone

A recent workshop comprised of the European Society of Paediatric Endocrinology, Growth Hormone Research Society, and Pediatric Endocrine Society determined that the safety profile of GH administration for indicated purposes (i.e. GH deficiency) was satisfactory (Allen, Backeljauw, Bidlingmaier et al., 2016). In contrast, GH administration is not advised for anti-aging in healthy elderly due to increased adverse events (Liu, Bravata, Olkin et al., 2007). However, there is little systemic evidence of adverse effects related to GH abuse in humans. Most accounts of side effects are anecdotal and/or are related to abuse of multiple substances. These effects are believed to be similar to those observed in acromegaly which may result in hypertension, carpal tunnel syndrome, diabetes, and neuropathy among many others (Table 1) (Pope et al., 2014, Ezzat, Forster, Berchtold et al., 1994, Wass JAH, 2002, Bengtsson, Eden, Ernest et al., 1988, Colao, Marzullo, Di Somma et al., 2001, Colao, Pivonello, Di Somma et al., 2007, Jenkins, Mukherjee and Shalet, 2006, Kreze, Kreze-Spirova and Mikulecky, 2001). Nevertheless, overuse/abuse may be associated with unknown side effects given that it is often used in combination with other agents and at higher doses. In animals, administration of GH in supraphysiologic doses leads to an increase in many organs, most noticeably, cardiomegaly, which also mimics that seen in acromegaly (Kopchick, Bellush and Coschigano, 1999, Penney, Dunbar and Baylerian, 1985). Edema, orthostatic hypotension, myositis, carpal tunnel, and gynecomastia have also been reported during GH administration to frail elderly (Cohn, Feller, Draper et al., 1993, Sullivan, Carter, Warr et al., 1998) while carpal tunnel and hyperglycemia were reported during GH administration to healthy adults (Blackman, 2004). Edema, decreased glucose tolerance, paresthesias, and in rare cases, macular degeneration were reported after GH administration during AGHD (Reed, 2013). The first documented report of rhGH abuse-induced diabetes was reported in 2007 when a 36-year old man with a presented to the emergency department with acute renal failure (Young and Anwar, 2007). The man admitted to a 15 year history of steroid abuse and 3 years of rhGH use. In addition, GH was originally extracted from the pituitary glands of human cadavers for treatment of short stature until its association with Creutzfeldt–Jakob Disease was discovered in 1985. Cadaveric GH is still available overseas and its use can potentially expose individuals to this deadly disease (Brown, Gajdusek, Gibbs et al., 1985).

Insulin-like growth factor-1

Most features of IGF-I misuse will not be distinguishable from those that develop from GH abuse, since IGF-I production is also promoted by increased GH levels. However, hypoglycemia, seizures, jaw pain, myalgia, edema, headaches, increased liver and kidney mass, and altered liver function among others (Table 2) have been reported after rhIGF-I administration (Sullivan et al., 1998, Williams, McDonald, O'Savage et al., 2008, Laron,

1999, Major, Laughlin, Kritz-Silverstein et al., 2010). The most common adverse side effects are erythema and lipohypertrophy at the injection-site (Williams et al., 2008).

Insulin

Hypoglycemia is the most common complication of insulin use. It is a dose-dependent effect of insulin and it occurs commonly in PED users since they tend to be individuals without diabetes or insulin resistance and do not use glucometers for capillary glucose measurements. It is also more likely to happen with the use of short-acting insulin or insulin analogs (i.e. lispro, aspart, regular, etc). Hypoglycemia can lead to loss of consciousness, coma, seizures, and potentially death. Insulin-induced hypoglycemia, seizures and severe chronic brain damage have been reported after prolonged neuroglycopenia in two cases after chronic use of insulin for doping (Elkin et al., 1997). In a different report of 41 insulin users, hypoglycemia was reported by most of the subjects (56.8%), and one individual reported unconsciousness (Ip, Barnett, Tenerowicz et al., 2012). Acutely, signs and symptoms of hypoglycemia are due to increased adrenergic tone (tachycardia, palpitations, anxiety, sweatiness, tremors) and neuroglycopenia (confusion, sleepiness, hunger, coma, seizures). Chronic hypoglycemia has been associated with hypoglycemia unawareness due to a decrease in adrenergic response and cognitive problems.

As with other injectable agents, improper aseptic techniques and unsafe use of needles can lead to skin infections, abscesses, and transmission of serious infections including hepatitis B and C and HIV (Larance, Degenhardt, Copeland et al., 2008). Insulin can also induce hypokalemia as it induces a shift of potassium into the cells leading to muscle cramping, respiratory paralysis, ventricular arrhythmias, and death. This may be particularly troublesome for individuals performing aerobic exercise which may have hypokalemia due to dehydration. As insulin also increases lipogenesis, it can lead to an increase in adiposity and overall weight gain. Other minor side effects include peripheral edema and the potential for bruising or localized lipodystrophy at the site of injection.

The impact of polypharmacy

The vast majority of individuals using anabolic agents for recreational purposes use more than one substance. Substances frequently used as supplements to AAS include alcohol, amphetamine, caffeine, cannabinoids, clenbuterol, cocaine, codeine, creatine, ephedrine, erythropoietin, gamma hydroxybutyrate, GH, heroin, human chorionic gonadotropin, insulin, IGF-I, tamoxifen, tobacco, and many others (Ip et al., 2012, Sagoe, McVeigh, Bjornebekk et al., 2015, Borjesson, Garevik, Dahl et al., 2016). In one US report of 41 insulin users, 95% also used AAS concomitantly and practiced polypharmacy by incorporating 16.2 ± 5.6 PEDs in their yearly routine (Ip et al., 2012). In the UK, polypharmacy of GH and AAS is increasing as production costs decrease with one third of AAS users reportedly also using GH (Hope, McVeigh, Marongiu et al., 2013, McVeigh and Begley, 2017). In addition, 1 in 8 female AAS users in Sweden, also reported GH use (Borjesson et al., 2016).

Unfortunately, AAS use can lead to dependence and usage of opioids and other illicit drugs unrelated to physical performance or fitness (Skarberg et al., 2009). In addition, use of

multiple off-label or black market substances can increase unrelated health risks. For example, a young multi-PED user recently died from severe arsenic poisoning from a contaminated pill bottle (Perera, Steinbeck and Shackel, 2013). While the arsenic exposure was the root cause of his symptoms, it is unclear how his multiple PED use exacerbated or hastened his ultimately fatal condition. Liver disease was reported in two other young multi-PED users; both regimens included GH and one also included insulin (Solimini, Rotolo, Mastrobattista et al., 2017). Polypharmacy is also reported in individuals who cycle (dose-stop-dose intervals) or pyramid (intervals of slow dosing and tapering) PED use as non-performance related substances such as are often required for transitioning off of PEDs (i.e. aromatase inhibitors) or to combat side effects of PEDs (i.e. medication to treat hair loss), namely from AAS use.

Conclusions

Although there is plenty of data on the anabolic potential of GH, IGF-I, and insulin and on their safety and efficacy at physiologic doses, most of this information comes from their therapeutic use in other settings (AGHD, diabetes), or from pathological disorders characterized by hormone hypersecretion (acromegaly, insulinoma). The majority of the data about the abuse of these and other PEDs comes from case reports or uncontrolled studies, underscoring the need for more research in this area. This would be challenging as randomized controlled studies would be unethical and certain subpopulations such as professional athletes may not be willing to volunteer information about PED use. Establishing a long-term prospective registry study has been suggested in a recent Endocrine Society Scientific Statement on this topic (Pope et al., 2014) and this could prove very valuable in determining the long-term safety of PEDs. Other challenges in interpreting the data available and designing future studies include the extremely high rate of polypharmacy and substance abuse linked to PED use.

In recent years, new formulations of GH (i.e. clinicaltrials.gov identifiers NCT01909479, NCT02693522, NCT01909479, NCT02229851, NCT02410356, etc.) and insulin (insulin degludec and insulin degludec/aspart) have completed phase III clinical trials or have been approved by the FDA. In addition, new compounds known to stimulate the release of GH, known as GH secretagogues or ghrelin mimetics, are also in clinical development (NCT02558829). As these drugs become commercially available more resources will be needed to develop commercially available tests to detect them. In addition, efforts to educate the medical community and the general public to recognize the deleterious effects of PEDs and to develop strategies to help individuals currently using PEDs are also desperately needed.

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Abbreviations

PED	performance enhancing drug
AAS	anabolic-androgenic steroids
PI3K	phosphoinositol 3-kinase
mTOR	mammalian target of rapamycin
FOXO3a	Forkhead boxO3a
MuRF-1	muscle RING finger 1
GSK3	glycogen synthase kinase 3
MGF	muscle-specific IGF-I
MAPK	mitogen activated protein kinase
IRS	insulin receptor substrate
P-III-NP	procollagen type III amino-terminal propeptide
ALS	acid-labile subunit

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Highlights

- PEDs are used professionally & recreationally but can be appropriately detected
- Evidence does not suggest that GH, IGF-1, or insulin doping enhances performance
- Community education is needed regarding negative side effects of recreational doping
- Many PED users engage in polypharmacy, increasing the risk of adverse health events

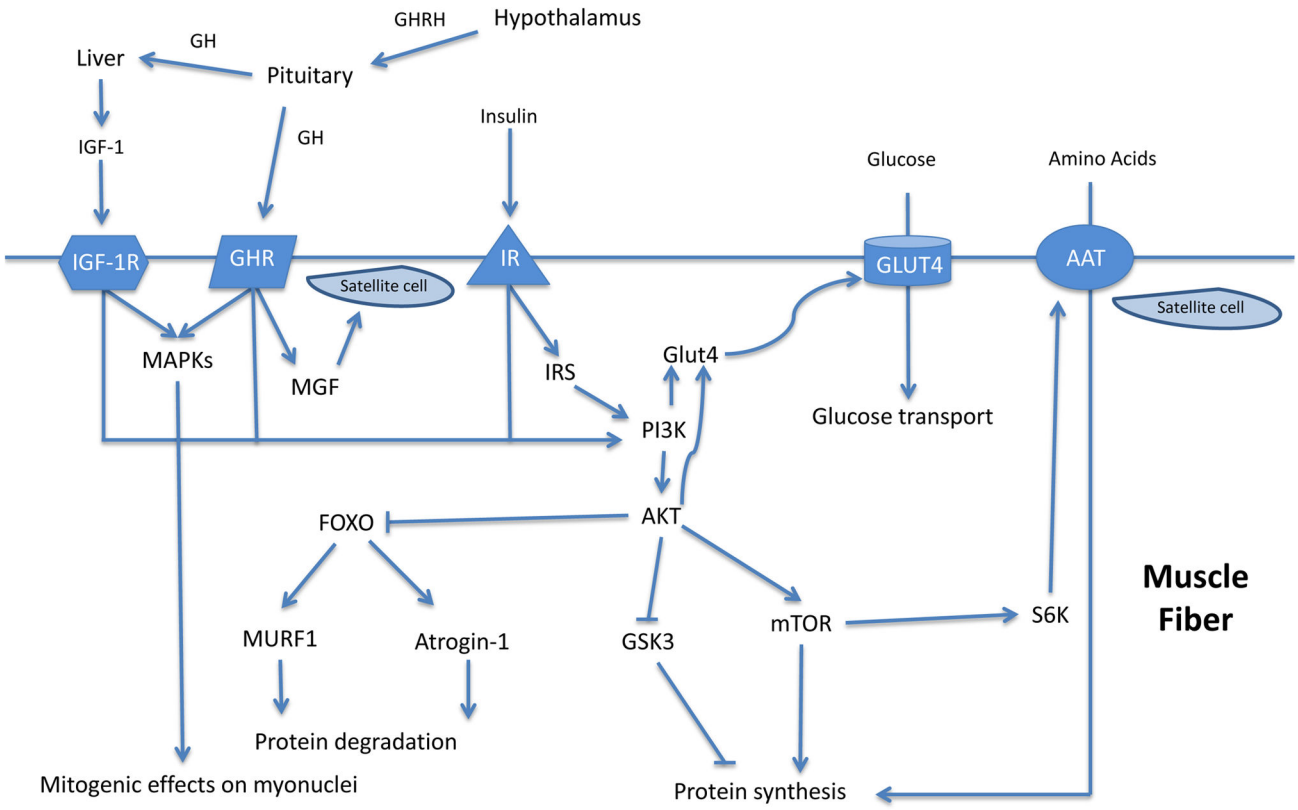

Figure 1. Mechanisms of action of GH, IGF-1, and insulin in skeletal muscle

AAT, amino acid transporter. Intramuscular anabolic mechanisms mediated by GH, IGF-1, and insulin providing the theoretical basis for use of these agents as PEDs.

Table 1

Side effects of excess GH due to disease, supplement, or use for anabolic purposes.

Organ System/Effect	Excess due to acromegaly	Physiologic Supplementation	Overuse/abuse
Cardiovascular/Lymphatic	Cardiomyopathy Hypertension	Excessive sweating Edema	Congestive heart failure Hypertension
Metabolic	Diabetes Insulin resistance	Decreased glucose tolerance	Diabetes
Neurologic	Peripheral neuropathy Sleep apnea	Paresthesia	
Musculoskeletal	Osteoarthritis Acral enlargement	Arthropathy Carpal tunnel Myositis	
Reproductive	Menstrual disturbance Erectile dysfunction	Gynecomastia	
Dermatologic	Coarsening of skin		
Increased Cancer Risk	Thyroid Colorectal		

Table 2

Side effects of excess IGF-I and insulin due to supplement or use for anabolic purposes.

Organ System/Effect	Physiologic Supplementation	Overuse/abuse
	IGF-I	
Cardiovascular/Lymphatic	Edema	Edema
Metabolic	Insulin resistance Orthostatic hypotension	Hyperandrogenism Hypoglycemia
Musculoskeletal	Myositis Arthralgia Jaw pain	
	Insulin	
Metabolic		Hypoglycemia
Neurologic		Loss of consciousness Coma Seizures Potentially death