Does Dihydrotestosterone Affect Physical Performance, Or Parameters Known To Affect Physical Performance Capacity Independently From The Effect Of Testosterone? A Protocol For A Systematic Review.

All authors are listed and have agreed to upload it to SportRxiv.

This is a preprint of the study protocol.

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Please cite as:

Hamilton, B., et al. (2024). "Does Dihydrotestosterone Affect Physical Performance, Or Parameters Known To Affect Physical Performance Capacity Independently From The Effect Of Testosterone? A Protocol For A Systematic Review." *Open Science Framework. DOI 10.17605/OSF.IO/VCQHB*

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Preprint
not peer reviewed

Does Dihydrotestosterone Affect Physical Performance, Or Parameters Known To Affect Physical Performance Capacity Independently From The Effect Of Testosterone? A Protocol For A Systematic Review.

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Abstract

Background: The role of hormones in human physical performance has been a subject of extensive research. Testosterone has been widely studied for its significant impact on muscle mass and muscle protein synthesis, strength, and physical performance. However, the role of dihydrotestosterone (DHT), a more potent androgen derived from testosterone in physical performance needs to be clarified, leading to a gap in the literature and creating an opportunity for a systematic review. **Aim:** To systematically review the existing literature to elucidate the independent effects of DHT on physical performance in humans and animal models, separate from the effects of testosterone. **Methods:** Studies published up to 31/07/2024 will be retrieved from three electronic sources (PubMed, Embase, SportDiscus). Keywords relevant to all searches will include “dihydrotestosterone or DHT", “performance", “human", and “animal”. This study will adhere to PRISMA guidelines. The primary *a priori* outcome measures will include changes in human performance, such as any laboratory or field assessment involving exercise (e.g., power, $\dot{V}O_{2max}$, force, torque, time, etc.) Secondary *a priori* outcomes in animal and human models will include parameters affecting physical performance capacity (e.g., [Hb], HCt, body composition and other anthropometric measurements including muscle mass, overall, regionally, stroke volume, hormones, gene expression, etc.).

1. Introduction

The role of hormones in human physical performance has been a subject of extensive research and debate [1-5]. Among these hormones, testosterone has been widely studied [1, 2, 6-10] for its significant impact on muscle mass and muscle protein synthesis [8], strength [9, 10], and physical performance [6]. However, the role of dihydrotestosterone (DHT), a more potent androgen derived from testosterone [11] in physical performance needs to be clarified, leading to a gap in the literature and creating an opportunity for a systematic review, which could identify gaps in understanding, challenge our understanding of the physiological basis of physical performance, and guide future research.

During typical male puberty, circulating testosterone increases substantially due to production by the Leydig cells in the testes [12], and is largely responsible for initiating male-specific pubertal increases in characteristics relevant to physical performance capability such as height and limb length, muscle mass and strength, blood haemoglobin concentration, and organ size [6]. Testosterone also continues to influence characteristics related to physical performance capability after puberty, as demonstrated by the consequences of low testosterone as a manifestation of hypogonadism in cisgender men [13]. Endogenous formation of DHT occurs primarily in certain peripheral tissues like skin, with most circulating DHT formed by the liver, mainly via conversion from testosterone by the cleaving action of the 5-alpha-reductase enzyme [14]. Whether, and to what extent, DHT plays an additional role beyond that of testosterone in initiating those pubertal changes related to physical performance, post-pubertal maintenance of physical performance capability, or modulating acute responses to exercise or influencing chronic adaptations to exercise training, is less clear. Certainly, DHT has been associated with aspects of physical performance in a variety of contexts and experimental models [15-18], is used therapeutically (often known as Androstanolone/Andractim) in certain circumstances [19, 20], and understandably is prohibited for athlete use at all times as an anabolic agent (anabolic androgenic steroid) by the World Anti-Doping Agency (WADA)[21]. However, exogenous administration of DHT that might elicit supraphysiological concentrations, and evidence from animal models, are not directly applicable to endogenous DHT production in humans. Therefore, a systematic review on this topic is warranted to evaluate the existing evidence.

2. Aim

This systematic review aims to systematically review the existing literature to elucidate the independent effects of DHT on physical performance in humans and animal models, separate from the effects of testosterone.

Objectives

The objectives of this study are as follows: Identify Relevant Studies, Conduct Rigorous Data Extraction, Perform Quality Assessment, Thoroughly Synthesize Data, Interpret Findings, and Discuss Implications.

3. Materials and Methods

Study Eligibility Criteria

The primary inclusion criteria will be employed, as shown in Table 1. Only studies that meet the requirements outlined in Table 1 will be included in the analysis. Primary searches will be limited to randomised controlled trials (RCTs) as the only way to ensure that understood confounders can be controlled and eliminate the overestimation described in non-RCTs [22, 23]. As this systematic review is interested in the independent effects of dihydrotestosterone (DHT) on physical performance in humans and animal models, studies with multiple interventions (e.g., DHT combined with testosterone) will only be included if there is a comparative control group. It is hypothesised that the primary search criteria will provide a low yield. Should a low study yield be presented from the primary search, a secondary search will be done using the same criteria as the primary one, including additional clinical trials, books, documents, and reviews. This systematic review will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [24, 25]. The protocol for this systematic review is registered on Open Science Framework (OSF) Registries (trial registration number [??]).

Table 1. Study eligibility criteria

Primary Inclusion Criteria
1) Randomised Trials With Comparative Control Group
2) Published In English, full text available
3) DHT investigated in Human Or Animal Performance Models
4) Published up to 31st July 2024
5) Laboratory or field assessment involving exercise (e.g., power, $V\dot{O}_{2max}$, force, torque, time, etc.)
6) Parameters affecting physical performance capacity (e.g., [Hb], HCt, body composition and other anthropometric measurements including muscle mass, overall, regionally, stroke volume, hormones, gene expression, etc.)
Secondary Inclusion Criteria
1) Clinical Trials, Reviews and Meta-Analysis
2) Published In English, full text available
3) DHT Investigated in Human Or Animal Performance Models
4) Published Up To 31st July 2024
5) Laboratory or field assessment involving exercise (e.g., power, $V\dot{O}_{2max}$, force, torque, time, etc.)
6) Parameters affecting physical performance capacity (e.g., [Hb], HCt, body composition and other anthropometric measurements including muscle mass, overall, regionally, stroke volume, hormones, gene expression, etc.)

Data Sources

Studies published up to 31/07/2024 will be retrieved from three electronic sources (PubMed, Embase, SportDiscus). Keywords relevant to all searches will include “dihydrotestosterone or DHT", “performance", “human", and “animal”. Based on PRISMA guidelines [24]. Upon completion, an example search strategy will be submitted as supplementary material. The first author (BRH) will conduct all electronic database searches. In addition to electronic database searches, cross-referencing from retrieved studies will also be undertaken.

Study Records and Selection

All studies will be imported into EndNote (EndNote 20, Clarivate Analytics, USA), and duplicates removed by the first author (BRH). A database copy will then be provided to the second author (DRM) for duplicate screening. The first and second authors (BRH and DRM) will select studies independently. Multiple studies will be handled by including only the most recently published articles. The screener(s) will not be blinded to journal titles or the study authors/affiliations. Reasons for exclusion will be coded based on one or more of the following: 1) inappropriate population, 2) inappropriate intervention, 3) inappropriate comparison(s), 4) inappropriate outcome(s), 5) inappropriate study design or 6) other. On

completion, the screeners will meet to discuss their selections and reconcile discrepancies by consensus. The last author (AGW) will provide a recommendation if an agreement cannot be achieved. Before reconciling any discrepancies, the agreement rate will be calculated using Cohen's ϰ statistic [26]. The precision of searches will also be calculated as the number of studies included divided by the number of studies screened (less duplicates) [27]. We will then calculate the number needed to screen (NNS) by taking the reciprocal of the precision [27]. A flow diagram of this process and a complete list of studies will be made available as supplementary material on submission of Stage 2.

Data Abstraction

The first (BRH) author will create an electronic code book before data abstraction, with feedback from all other authors. The study characteristics (e.g., author, journal, year, etc.), participant characteristics (e.g., age, height, mass, etc.), intervention details (e.g., type, length, frequency, etc.), and outcome characteristics (e.g., sample sizes, baseline/post-intervention means and SDs, etc.) will be the primary categories used to code the data. All data will be extracted independently by the first (BRH) and second (DRM) authors, who will then convene to settle any differences by consensus. If this is not feasible, the last author (AGW) will offer a suggestion. Before this, Cohen's statistic ϰ [26] will be used to determine the overall agreement rate.

Outcome Measures

The primary *a priori* outcome measures will include changes in human performance, such as any laboratory or field assessment involving exercise (e.g., power, $V\dot{O}_{2max}$, force, torque, time, etc.) Secondary *a priori* outcomes in animal and human models will include parameters affecting physical performance capacity (e.g., [Hb], HCt, body composition and other anthropometric measurements including muscle mass, overall, regionally, stroke volume, hormones, gene expression, etc.) Obtaining missing data will be attempted for all primary and secondary outcome measures if assessed by a study. The corresponding author of any study with the missing data will be contacted three times via email by the first author (BH), with one week between each communication. These communications will be tracked (e.g., dates, responses, success rates, etc.) to establish the success rate of this process.

Risk of Bias Assessment

The risk of bias for the randomised control trials from primary inclusion criteria will be assessed using the recently revised Cochrane Risk of Bias instrument for randomised controlled trials (RoB 2) [28]. Using one or more signalling questions, the RoB 2 instrument assesses the risk of bias in five distinct domains: (1) bias arising from the randomisation process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome, and (5) bias in the selection of the reported result. Based on signalling questions, each domain is assessed as “low risk”, “high risk”, or “some concerns”. Based on responses to each domain, each study's overall risk of bias will then be assessed as either “low risk”, “high risk”, or “some concerns”. Rob 2 was

chosen over the various study quality instruments as the RoB 2 is more robust in differentiating between the quality of reporting and the quality of the conduct of a study [28]. Risk of bias in non-randomized follow-up studies of interventions (ROBINS-I [29]) will be used to assess intervention studies. Based on responses to each domain, each study's overall risk of bias will then be evaluated as either "low risk", "moderate risk", "Serious risk", "critical risk", or "no information". No studies will be excluded from the analysis based on their risk of bias assessment. The first (BRH) and second (DRM) authors will undertake the risk of bias assessment independently of one another before meeting to resolve any discrepancies by consensus. The last author (AGW) will recommend where this cannot be achieved.

4. Contributions

Conceptualization, BRH and AGW; methodology, BRH; writing (original draft preparation) BRH and AGW, writing (review and editing), ALL

5. Funding Information

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

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