The application of trimetazididine in healthy individuals: a systematic review

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Abstract. – OBJECTIVE: Currently, there is no evidence to support trimetazididine (TMZ) administration aimed at enhancing physical performance or post-exercise recovery in healthy individuals or athletes from the general and athletic populations, respectively. Considering the lack of empirical data, from a scientific and practical perspective, it would be interesting to review research with high methodological quality that examines the effects of TMZ on healthy individuals and athletes from various age groups.

MATERIALS AND METHODS: Data sources included English articles that were initially searched by keywords utilizing PubMed, Scopus databases, and the Cochrane Library and published prior to November 2022. Thus, a systematic review of the scientific literature was performed with a traditional PRISMA methodology. An initial keyword search found 2,673 publications, and further screening selected 66 articles, of which only two articles met the inclusion criteria.

RESULTS: Two trials examining the effect of TMZ on healthy members of the general population that were published in 2017 and 2019 were analyzed. Publications examining athletes were not recruited for this analysis.

CONCLUSIONS: Currently, there are no data reporting a positive effect of TMZ on physical performance, post-exercise recovery, or other health parameters in members of the general population, while its administration is associated with the development of relatively common adverse effects.

Key Words: Trimetazididine, Athletes, Healthy volunteers, Doping, Performance, Post-exercise recovery.

Introduction

Modern elite sports places high demands on the human body, promoting the regular introduction of new methods and substances aimed at improving physical performance and post-exercise recovery. One of the most commonly employed methods to improve athletic performance is the administration of various pharmacological substances, biologically active supplements, and nutraceuticals. Various data suggest that the majority (40-100%) of elite athletes use or have used biologically active food supplements¹³, moreover, elite athletes use food supplements more often than their non-elite colleagues⁴. The average quantity of used food supplements is 1.7 to 3.4 per single athlete throughout the competitive season¹⁵. Currently, there is a number of proven substances that positively affect various aspects of physical performance, however, there is also an association with adverse health risks.

Such methods and substances have been included on the World Anti-Doping Agency (WA-DA) prohibited list, established in 1999 to provide
doping-free participation in competitions. To be included on the prohibited list, a method or substance must satisfy a minimum of two of the following three criteria:

• Potential enhancement of sports performance.
• Potential health risk.
• Violation of the sporting spirit.

At present, the WADA prohibited list contains over 20 classes of prohibited methods and substances, while only six are proven to positively affect physical performance. These are known as anabolic agents, growth hormones, stimulators, beta-agonists, androgen receptor modulators, and some metabolic drugs. According to Heuberger et al., trimetazidine (TMZ) is a substance that has no proven efficiency in healthy individuals, although it is still included in the Hormones and Metabolic Modulators class S4 section of the WADA list, which has been previously prescribed for managing angina. Trimetazidine was originally developed in 1963 by Servier Company, (Suresnes, Île-de-France, France), although nowadays, there are more than 30 commercial names for TMZ drugs. Trimetazidine is produced in capsule or tablet form with an instant or extended release, and the quantity of TMZ per unit varies from 15 to 80 mg.

Trimetazidine action implies partial inhibition of beta-oxidation of fatty acids by selective inhibition of 3-ketoacyl-CoA thiolase enzyme in cardiomyocytic mitochondria, resulting in the intensification of glucose oxidation and acceleration of glycolysis with glucose oxidation. This mechanism is thought to protect the myocardium from ischemia and cell damage by the products of lipid peroxidation. In the majority of countries, TMZ is used to stabilize angina as a combination therapy and secondary treatment. In other countries, TMZ is also registered to treat chorioretinal vascular disorders and tinnitus.

Despite TMZ being known for decades, it has only been named as a prohibited competition substance (Stimulators class S6 section) since January 1st, 2014, and banned since January 1st, 2015 (Hormones and Metabolic Modulators class S4 section). The first athletes suspended for TMZ usage were cyclic sport athletes. Additionally, in recently published scientific literature (prior to 2020), no study demonstrated the efficiency of TMZ on any aspect of physical performance or post-exercise recovery in healthy individuals of the general population.

Considering the lack of empirical data, from a scientific and practical perspective it would be interesting to review research with high methodological quality that examines the effects of TMZ on healthy individuals and athletes from various age groups. A further aim of the study is to determine the range and rate of adverse effects following TMZ administration.

**Materials and Methods**

The scientific literature search was conducted utilizing the PubMed and Scopus databases, and the Cochrane Library to identify trials addressing the effects of TMZ on healthy subjects. The search was conducted in accordance with the PRISMA guidelines.

Literature screening was performed in November 2022 using the following search request: (Trimetazidine Dichlorhydrate OR Trimetazidine Dihydrochloride OR Trimetazidine Hydrochloride OR Trimetazidine) AND (athletics OR sports OR human OR animal OR endurance OR strength OR speed OR coordination OR “cognitive functions” OR recovery OR hypoxia OR contamination OR wada OR doping OR training OR competitions OR performance OR “adverse event” OR “side effect” OR efficacy OR effectiveness OR adolescents OR children OR “extreme ambient conditions” OR “military medicine” OR “military personnel” OR “Mixed martial art”) AND NOT (surgery OR angina OR infarction OR tinnitus OR heart failure OR combination). All discovered and eligible articles were examined. To formulate eligibility criteria, PICOS was used. The inclusion criteria were:

1) The article is a clinical study.
2) The subjects of the study were healthy individuals.
3) The research focused on the effects of TMZ on the body.
4) The intervention was the use of TMZ vs. placebo.

In addition, the selection of articles was based on a detailed review of studies in which:

1) The intervention was carried out on animals.
2) The determination of TMZ in the blood and urine of healthy volunteers was studied.
3) The side effects of TMZ were described.
All identified studies have been assessed for risk of bias using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)\(^1\). Cases of disagreement in assessments of the risk of bias between the reviewers were resolved by discussion or with consultation with a third reviewer if warranted.

**Results**

Keyword searches identified 2,673 publications. Twelve articles were excluded as the literature was not in the English language. Title and abstract screening selected 66 articles that were thoroughly examined for eligibility using the inclusion criteria (Figure 1).

The excluded articles are one clinical case, one literature review and two uncontrolled studies. Twenty-five articles dedicated to the methods of TMZ detection rather than its beneficial effects, 15 articles used animals as subjects, and 9 articles assessed TMZ safety and tolerability were also excluded from the analysis. In summary, only two randomized controlled trials\(^6,17\) (RCTs) examined the effect of TMZ on healthy volunteers who were not elite athletes, published in 2017 and 2019, studies of high methodological quality (Table I).

From the analysis performed, the risk-of-bias in the study by Yang et al\(^6\) was low, and the

![Figure 1. Selection of studies.](image-url)
The application of trimetazidine in healthy individuals: a systematic review

The results of the present review identified only two studies examining the use of TMZ in healthy individuals representative of the general population. In these studies, the time period for TMZ usage was short (5 and 20 days), while no studies investigated individuals in specific conditions (elite athletes, military personnel, ballet dancers, etc.), suggesting the lack of TMZ support in such environments.

Yang et al. examined 39 randomized volunteers administering 20 mg of TMZ or a placebo three times a day (20 and 19 subjects, respectively) for two weeks post-treatment and examined a number of cardiorespiratory parameters. Following the acute shift in altitude (400 m above sea level to 3,400 m above sea level without acclimatization) no inter-group differences were seen in any analyzed parameters after TMZ administration during 14 days at the lowland. Course of TMZ treatment did not significantly protect from altitude disease, but effectively reduced fatigue upon acute high-altitude exposure and improved a number of parameters of cardiorespiratory fitness and post-exercise recovery at the altitude of 3,400 m above sea level.

Al-Kuraishy et al. examined 234 subjects (120 men and 114 women) aged 22-25 years, TMZ treatment significantly affected all psychomotor parameters and critical flicker-fusion frequency ($p < 0.001$) compared to the pretreatment period regardless of gender.

Table I. Studies investigating the effect of trimetazidine use in healthy volunteers.

<table>
<thead>
<tr>
<th>Title</th>
<th>Subjects</th>
<th>Dose</th>
<th>Treatment duration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. 2019</td>
<td>39 men, 17-24 years old, living at lowland</td>
<td>20 mg</td>
<td>20 days (14 days before ascending) 3,000 meters and 6 days after ascending</td>
<td>No statistical differences were seen in any analyzed parameters after TMZ administration during 14 days at the lowland. Course of TMZ treatment did not significantly protect from altitude disease, but effectively reduced fatigue upon acute high-altitude exposure and improved a number of parameters of cardiorespiratory fitness and post-exercise recovery at the altitude of 3,400 m above sea level.</td>
</tr>
<tr>
<td>Al-Kuraishy et al. 2017</td>
<td>234 subjects (120 men and 114 women) 22-25 years old</td>
<td>15 mg per day</td>
<td>5 days</td>
<td>TMZ treatment significantly affected all psychomotor parameters and critical flicker-fusion frequency ($p &lt; 0.001$) compared to the pretreatment period regardless of gender.</td>
</tr>
</tbody>
</table>

Discussion

The results of the present review identified only two studies examining the use of TMZ in healthy individuals representative of the general population. In these studies, the time period for TMZ usage was short (5 and 20 days), while no studies investigated individuals in specific conditions (elite athletes, military personnel, ballet dancers, etc.), suggesting the lack of TMZ support in such environments.

Yang et al. examined 39 randomized volunteers administering 20 mg of TMZ or a placebo three times a day (20 and 19 subjects, respectively) for two weeks post-treatment and examined a number of cardiorespiratory parameters. Following the acute shift in altitude (400 m above sea level to 3,400 m above sea level without acclimatization) no inter-group differences were found, although the cardiorespiratory parameters in the TMZ group significantly increased when compared to the placebo group. Despite these clear differences, these data poorly apply to athletic activities with the possible exception of mountain sports. This may be partly explained...
by and associated with the climatic condition of altitude (3,400 m in the Yang et al study), as no training or competitions are organized in such conditions except for certain extreme sports. Furthermore, if training and highland living at an altitude of 2,000-2,500 m is included in the preparation program of athletes with the aim of creating conditions for the pre-conditioning of muscles, cardiovascular system, and blood under relative oxygen deficiency, this may prove beneficial. Furthermore, the TMZ application reduces the contribution of relative hypoxia and alleviates the altitude effects.

The second study17 performed in healthy individuals was not directly related to the analysis of functional parameters and, therefore, could not provide a reliable source of information regarding TMZ efficiency. Al-Kuraishy et al17, determined the influence of five days of TMZ administration on psycho-motor reactions. The authors demonstrated that such a dosing regimen may improve psycho-motor performance and vigilance in normal healthy volunteers by improving reaction time and critical flicker-fusion frequency.

Two uncontrolled studies18-19 published in 1985 and 1993 were also analyzed in detail. In the study by Maridonneau-Parini I et al18 seven volunteers who consumed TMZ for seven days showed a decrease in indices characterizing the severity of erythrocyte damage by peroxidation products. However, no functional parameters were assessed. Furthermore, Devynck MA et al19, supplemented blood, previously taken from healthy volunteers and patients with arterial hypertension, with TMZ. In vitro the TMZ effects were shown in ADP-induced (Adenosine diphosphate-induced) platelet aggregation and adenylyl cyclase activity, which did not represent the functional parameters analyzed.

An important issue for administering any pharmacological substance is safety and tolerability. According to Food and Drug Administration (FDA) guidelines20, all side effects can be classified as very common, common, uncommon, rare, and very rare. The adverse effects rate is between 1 and 10 cases per 100 administrations, and this is considered common. Our research only examined trials of high methodological quality reporting the rate of adverse effects in the clinical administration of TMZ in patients with cardiovascular diseases. Three of the largest trials21-23 assessing the efficiency of TMZ (2,026 patients) reported only 5% (101 patients) with unfavorable effects. The most common side effect described included nausea or vomiting (1.73%), dry mouth or hot flushes (0.74%), headache (0.64%), diarrhea or distension (0.35%), sleep disturbances (0.30%), and weakness or fatigue (0.25%)24. Further studies25-27 reported parkinsonism, tremors, and gait impairment during TMZ administration.

The safety of any food supplement and medication used by elite athletes against unintentional doping is crucial. Since TMZ is a prohibited substance and its detection in doping tests is followed by long-term suspension of up to four years, contamination with trimetazidine is a significant problem. According to available data28, contamination of biologically active supplements and nutraceuticals with prohibited substances not listed on the substance label is common and varies between 12% and 58%. Duiven et al29 demonstrated that 38% of food supplements bought online (21 brands in 17 online shops) contained undeclared banned substances, including consistently prohibited items listed by WADA, such as anabolic steroids and metabolic modulators, which if found in a tested sample is punishable by a two-to-four-year suspension.

Contamination of any food product or WADA-accredited medication with prohibited substances is also possible. However, unlike the established data on the contamination prevalence of biologically active supplements, information regarding the contamination of food and permitted drugs with prohibited substances resulting in Adverse Analytical Findings (AAF) is scarce and predominantly confined to substances such as anabolic agents [clenbuterol, exogenic anabolic steroids, and selective androgen receptor modulators (SARMs)] and diuretics30-35. Regarding other prohibited substances, only single cases have been described in the literature36 and thus this quantity is unlikely to grow extensively. For example, cases of food contamination with furosemide and letrozole have been previously reported, where athletes escaped suspension due to mitigated circumstances by re-assuring the disciplinary board of an unintentional administration of the prohibited substances.

Although, in some cases, official drugs permitted for athletes were found to be contaminated with prohibited substances not documented on the substance label. Helmlin et al37 described such an individual case in 2016, where the coating of ibuprofen, a non-steroid anti-inflammatory drug, contained trace elements of a banned substance, diuretic hydrochlorothiazide, that resulted in a disciplinary proceeding, although
eventually, the athlete was acquitted. There are currently only two documented cases\textsuperscript{38,39} in the existing literature where TMZ contaminated a biologically active supplement and a multi-vitamin complex. Furthermore, in 2016 an American swimmer was suspended for two years for doping. The positive TMZ test was conducted out-of-competition period. The Hearing Panel of FINA International Swimming Federation upheld the existence of the sanction as the athlete failed to list the likely source of this substance in the tested sample. Nonetheless, finally the athlete managed to prove that the vitamin and mineral complex contained TMZ and the Court of Arbitration for Sport confirmed the two-year suspension to six months. Furthermore, during the 2018 Olympic Games in Korea, TMZ was discovered in the doping test sample of a Russian bobsledder. The Olympic results were revoked, and this athlete was disqualified for eight months. Later the athlete managed to prove that methionine amino acid, an authorized drug that had been consumed, contained trace elements of TMZ and thus had unknowingly ingested this prohibited substance. The information concerning the presence of TMZ was not listed on the drug label. Therefore, in October 2018, the Court of Arbitration for Sport confirmed that the athlete received the prohibited substance involuntarily and thus re-instated the athlete to continue competing.

Finally, it should be emphasized that the detection of TMZ in doping tests is currently exclusive, and the majority of cases involve athletes from cyclic sports. Thus, according to the 2019 WADA report\textsuperscript{40}, the detection of TMZ in doping tests was associated with only five (five from 362) AAFs. This is only 1% of documented cases referred to the Hormone and Metabolic Modulators class S4 section, which includes TMZ. Furthermore, substances of this class such as tamoxifen, meldonium, and clomifene were identified as AAFs in doping tests on 80, 79, and 73 occasions respectively, during 2019\textsuperscript{40}. Moreover, notably the current systematic review did not detect any trials investigating the influence of TMZ on any health or physical performance parameters in people above 18 years old.

Considering the limited practical application of TMZ, even prior to its prohibition (0.1% - 0.23% of total tests analyzed in anti-doping laboratories until 2010), it is reasonable to conclude that TMZ application has been scant\textsuperscript{41,42}. However, it is important to note that for athletes who are subjected to regular testing, a course of TMZ treatment is extremely complicated, as athletes have to regularly update the Anti-Doping Administration and Management System (ADAMS) system with their location and are must always available for testing by the National Anti-Doping Organizations and International Sports Federation. Furthermore, since the TMZ measurement threshold in urine is 0.5 ng/mL in WADA-accredited laboratories, and this concentration is detectable for a minimum of five days even after a single use, the intentional TMZ administration by athletes is completely unreasonable and associated with an extremely high risk of long-term suspension. Together with the absence of empirical scientific data supporting TMZ efficacy for healthy people as a pharmacological agent to improve exercise tolerance, this allows the conclusion that TMZ administration is not advisable.

Conclusions

To conclude, currently, there is no evidence to support TMZ administration aiming to enhance any parameter of physical performance or post-exercise recovery in healthy individuals and athletes. The prevalence of TMZ application, even prior to its prohibition, is scarce and confined to cyclic sports athletes. No published TMZ studies examined children and adolescents under 18 years old. The administration of TMZ may lead to the development of adverse effects, including those associated with impaired coordination and loss of movement precision.

Conflict of Interest
The Authors declare that they have no conflict of interest.

Ethics Approval and Informed Consent
Not applicable.

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No funding to declare.

Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
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