Red wine polyphenols improve cardiometabolic risk in obese subjects by alleviating inflammation and microvascular dysfunction

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Primary Objective: To study effects of RWPs on insulin sensitivity, glucose tolerance, microvascular function (skin and muscle), insulin-mediated microvascular responsiveness, and blood pressure.Secondary objectives: To study effects of RWPs on...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON39376

Source
ToetsingOnline

Brief title
The effects of red wine polyphenols on microvascular function

Condition

- Coronary artery disorders
- Glucose metabolism disorders (incl diabetes mellitus)
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
microvascular dysfunction, small vessel disease

Research involving

Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: nederlandse hart stichting

Intervention

Keyword: microvascular dysfunction, obesity, Red wine polyphenols

Outcome measures

Primary outcome

insulin sensitivity will be assessed during a hyperinsulinemic-euglycemic

clamp.

Skeletal muscle perfusion measured by contrast-enhanced ultrasonography before

and during hyperinsulinemia/meal test.

skin microvascular function (capillary microscopy and laser-doppler fluxmetry

with iontophoresis)

trancutaneous quadriceps muscle biopsy . Using Western blotting,

phosphorylation of relevant molecules in the insulin signaling cascade will be

assessed.

Secondary outcome

24-hr ambulant blood pressure measurement

markers of low-grade inflammation (hsCRP, fibrinogen, IL-6, TNF-alpha) and

adipocytokines (circulating whole-adiponectin, leptin).

Study description

Background summary

The global epidemic of obesity is bringing in its wake a catastrophic increase in the prevalence of metabolic diseases. As a result, obesity-related diseases, such as diabetes, hypertension, dyslipidaemia have surpassed tobacco use as a cause of death(1;2). Obesity is a major cause of insulin resistance, which has been implicated in the rising prevalence of the metabolic syndrome, a cluster of risk factors which confers an increased risk for type 2 diabetes and cardiovascular disease (CVD)(3). The mechanisms underlying this clustering are incompletely understood. Obesity-associated microvascular dysfunction explains part of this clustering and predisposes obese subjects to CVD(4;5). Microvascular dysfunction, by affecting both flow resistance and perfusion, is important not only in the development of obesity-related target-organ damage in the heart and kidney, but also in the development of cardiovascular risk factors such as hypertension and insulin resistance (6-9).

Beneficial effects of moderate use of alcoholic beverages (10), red wine in particular (11), on
cardiovascular disease have been acknowledged for many years. In addition, however, there are reported beneficial effects on components of the metabolic syndrome (MS). Most impressive of these have been the reported effects of moderate alcohol use on the incidence type 2 diabetes mellitus (DM). Epidemiological studies suggest an impressive 40 to 60% crude reduction in DM incidence.(12;13) This preventive effect is largely maintained (RR estimate: ~30%) after multivariable adjustment for possible confounders.(14)

The potential hazards of regular alcohol use are obvious. Thus, a key issue is to identify the
favourable components of alcoholic beverages, red wine in particular. In this context, several leads point to Red Wine Polyphenols (RWPs). Firstly, multiple experimental studies have shown beneficial effects of mixed or separate RWPs (i.e. without alcohol) on cardiometabolic parameters associated with obesity. (15-20) In addition, studies using pure alcohol have failed to confirm that alcohol itself is beneficial. In fact, alcohol may reduce insulin secretion and thereby partially offset the favourable effects of red wine on glucose homeostasis (21), eventually resulting in increased rates of DM as alcohol intake increases.(22) Finally, observations of favourable effects, similar to those of RWPs, of other polyphenol-rich food stuff, such as cocoa and green tea (23) point towards favourable effects of
polyphenols rather than of the alcohol component of red wine.

Recently, a freely available RWP mix (Provinols*) was administered to obese Zucker rats and
dramatically improved several parameters of glucose homeostasis.(17) Data in humans, however, are remarkably scarce. A small study in DM patients (n=9) suggested that red wine (not the RWP fraction in specific), improved insulin-mediated glucose disposal by an impressive 43%.(24)

As for the specific polyphenol components of red wine, most research has

focused on resveratrol and quercetin. Resvertrol is quite specific to red wine and has, at least in animal studies, beneficial effects on insulin sensitivity, insulin secretion, and endothelial function.(18;19) Quercetin, another dominant RWP compound, has also been implicated in RWPs favourable cardiometabolic effects.(18) Ina recent study, quercetin attenuated atherosclerosis in ApoE*/* gene*knockout mice by alleviating inflammation and improving NO bioavailability. (25) Red wine polyphenol powder had beneficial effects on the coronary microcirculation in patients with coronary artery disease (26). Interestingly, another
study showed that RWPs improve endothelial NO-mediated relaxation using the same PI3-kinase/Akt pathway as does insulin.(16) In addition, another study suggested that the RWP resveratrol acts to reduce endothelin expression.(27) Hence, a more favourable balance of insulin*s vascular effects by relative amplification of insulin*s activation of nitric oxide is conceivable. In part, these effects may be mediated by activation of Sirtuin 1 (SIRT-1) and AMP-activated protein kinase (AMPK) by RWPs.(15)

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Study objective

Primary Objective: To study effects of RWPs on insulin sensitivity, glucose tolerance, microvascular function (skin and muscle), insulin-mediated microvascular responsiveness, and blood pressure.
Secondary objectives: To study effects of RWPs on markers of low-grade inflammation, and couple the effects of RWPs to changes in the vascular insulin signaling cascade.

Study design

randomized controlled trial (double blind)

Intervention

mixed RWP 600mg/day (Provinols*, SEPPIC-France; corresponds to polyphenol content of 6 glasses of red wine) or matching placebo for a total duration of 8 weeks

Study burden and risks

We expect that volunteers who have been using the RWP will have a health benefit by volunteering for this study, however this health benefit is not direct noticeable. The volunteers will be compensated for their time and effort, as well as the invasive procedures, they will receive a total of ¤500 after completion of the investigations. Volunteers will also receive a compensation for their transport-costs.

The obese volunteers in this study are needed as they are supposed to be insulin resistant and have mild microvascular dysfunction.

Mixed RWP 600mg/day (Provinols*, SEPPIC-France; corresponds to polyphenol

content of 6 glasses of red wine, freely available) are composed of polyphenols of Carbernet-Sauvignon red wine and selected for its antioxidant content. It is an additive-free food product, obtained through simple physical extraction. No side effects have been reported yet. However a small risk (e.g. allergic reaction) is always present.

Risks of the hyperinsulemic-euglycemic clamp consist of nausea, headache afterwards and allergic reactions; rare: (self-limiting) flushing, urticaria and nausea, very rare: (<1:10.000) anaphylactic shock to one of the components of the insulin solution (saline 0.9%, Glucose 20%, insulin (NovoRapid®, Novo nordisk), Furthermore there is an obvious risk of hypo- (and hyper-) glycaemia, which will be counteracted by drawing regular blood samples and adjusting the glucose infusion rate.
Otherwise the risks are the same as those of a normal peripheral line, with failure of placement and repetitive attempts, a hematoma or phlebitis (1/100) being the most common. In the literature, clamping is a frequently used method, however, no adverse events are described as such. In this research unit, there is ample experience with clamping, no adverse events other than those mentioned before are known, phlebitis has occurred only once as the most serious adverse event in >200 (estimated) clamps performed over the previous years. Total blood sampling volume during the clamp ~40 ml.
The drawing of blood samples has a risk of a hematoma, slight pain at the insertion site during, and after the insertion, as well as the risk of failure and thus repetitive attempts.
Drawing blood samples from a venous catheter has the risk of quick thrombus formation. Patency is checked regularly and forming thrombi are removed as soon as possible (the 3 way connector set-up makes this possible without the risk of injecting thrombi intravascular).

Risks associated with the meal test only consist of the above described risk during blood sampling. Total blood sampling volume during the meal test ~200 ml.

During CEUS we will make use of contrast (SonoVue ® microbubbles). The most common side effects with SonoVue (seen in between 1 and 10% of subjects undergoing studies with SonoVue) are headache, facial flushing, nausea, dizziness, moderate hypotension, injection site pain, injection site reactions, including bruising, burning, and paraesthesia at the injection site.
In a postmarketing study, serious adverse events occured in 0,009% of patients (2/23188). The serious adverse events consisted of dyspnoea, bronchospasm, slight hypotension and bradycardia in one patient who recovered in 30 minutes, the other serious adverse event consisted of clouding of consciousness, dorsolumbar pain, severe hypotension and a cutaneous rash, which lasted for 30 minutes. No fatalities occurred

Our own department has several years of experience with CEUS and SonoVue ® for research purposes. The department of anaesthesiology has several years of experience with MCE

During Capillary video microscopy and iontophoresis of acetylcholine and SNP along with laser Doppler measurements can cause in a minority of patients- a slight tingling feeling in the finger where iontophoresis is performed, because of the electric current used.

Risks associated with the quadriceps muscle biopsy include myalgia, cutaneous infection and bleeding at the biopsy site, to prevent the latter, adequate pressure will be applied as well as steri-strips and compressive bandages. Infections will be prevented by using sterile instruments and covers, as well as disinfecting the skin using chlorhexidine.

As the above mentioned side effects are well known, care will be taken throughout the protocol to prevent them from occurring (for example, adequate application of pressure at the cannulation sites after removal of catheters or frequent sampling of plasma glucose levels after initiation of insulin infusion (and adequate co-infusion of glucose) to prevent hypoglycaemia).

Volunteers will stay at the clinical research unit for at least 30 minutes after completion of all procedures in order to monitor any delayed adverse events. Volunteers are studied in the immediate vicinity of a clinical unit, where resuscitation facilities are present and can be at the bedside within 1 minute.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Obese (BMI *30)
Age 18-70 years
Caucasian

Exclusion criteria

cardiovascular disease
diabetes mellitus
recent history (<12 months) of high alcohol use > 4 U/day
use of medication potentially affection insulin sensitivity or microvasculair function
pregnancy
smoking

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-05-2012
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	05-12-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT01518764
CCMO	NL37147.029.11