# Effects of glutamine and epigallocatechin-3-gallate on glucose tolerance, markers of inflammation, oxidative stress and procoagulant status in Type 2 diabetes mellitus

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In this pilot study, the objective is to show an improvement in glucose tolerance,a decrease in parameters for inflammation, oxidative stress and a procoagulant state after 4 weeks of daily supplementation of L -glutamine and Epigallocatechin-3-...

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| **Ethical review** | Not approved |
| **Status** | Will not start |
| **Health condition type** | Diabetic complications |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON38189

**Source**
ToetsingOnline

**Brief title**
Glutamine and EGCG in type 2 diabetes mellitus

### Condition

- Diabetic complications

**Synonym**
diabetes, Type 2 diabetes mellitus

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Medisch Centrum Alkmaar
**Source(s) of monetary or material Support:** Onderzoeksgelden Dr A.P.J. Houdijk en subsidie MCA

## Intervention

**Keyword:** epigallocatechin-3-gallate, glutamine, Inflammation, type 2 diabetes mellitus

## Outcome measures

### Primary outcome

Primary study parameters:

Insulin sensitivity, by using an OGTT

### Secondary outcome

Secundary study parameters:

Other inflammatory parameters (CRP,IL-6, IL-18, TNF-*, leucocyte NFkappaB,

IL-4, IL-10). IL-6 en TNF-* na vol bloed LPS stimulatie.

Oxidatieve stress parameters(Malondialdehyde, TBARS, 8-iso-prostaglandin F2*).

Endothelial dysfunction parameters (VCAM-1, E-selectin, ICAM-1, vWF, cGMP,

nitrate/nitrite).

Pro-coagulant state (PAI-1, fibrinogen, P-selectin)

Body composition (BIA).

Weight changes

# Study description

### Background summary

In this pilot study the individual and combined effect of glutamine and epigallocatechin-3-gallate will be studied on glucose tolerance, inflammatory

and oxidative stress parameters and procoagulant state in newly diagnosed type 2 diabetics.
It is a prospective randomized single center 4 arms intervention study including 30 patients in each arm. Patients are 18 years and older with newly diagnosed type 2 diabetes with two times a post absorptive glucose of > 7mmol/l. Although, patients with a post absorptive glucose * 15 mmol/l or * 10 mmol/l and hyperglycemic complaints (polydipsia, polyuria, weight loss more that 10% in the last month) will be excluded.
For a duration of 4 weeks the effects of daily supplementation of L-glutamine (GLN, 0.3-0.5 g/kg/day) with epigallocatechin-3-gallate (EGCG, 3 x 150 mg) versus control (no intervention) will be studied on glucose tolerance, parameters for the inflammatory and oxidative stress response and parameters for a procoagulant state. During the 4 weeks of supplementation no diet or lifestyle interventions will be started. After the supplementation period patients will immediately start with diet and lifestyle interventions.
Background of the study.
In the year 2025, the number of patients with type 2 diabetes is expected to reach 1.3 million (RIVM 2007) taking into consideration the increase in aging and obesity. This calls for new affordable treatment modalities focusing on prevention of diabetes and its complications.
This study investigates the effects of two well known nutritional supplements, L-glutamine and EGCG, on inflammatory and oxidative markers and procoagulant state in newly diagnosed type 2 diabetes. The oxidative stress in type 2 diabetes is thought to underlie the atherosclerotic vascular changes typical for organ dysfunction. The significant lower level of glutamine in diabetics is related to reduced anti-oxidant capacity and impaired immune function, increasing the risk for infections. L glutamine supports endogenous antioxidant capacity via the production of glutathion and EGCG supports exogenous anti-oxidant capacity. In addition to these effects, glutamine and EGCG also have been reported to cause weight loss in the overweight which may reduce adiposity related type 2 diabetes. The potential efficacy of glutamine and EGCG is based on extensive in vitro, ex vivo, animal experimental, clinical and epidemiological research data of each individual molecule. The focus of these studies has been on insulin production and resistance, glutathion production, the anti-oxidative and anti-inflammatory effect. The hypothesis is that the reduction in oxidative and inflammatory stress that can be achieved with both L-glutamine and EGCG will result in better glusose homeostasis and less endothelial damage preventing micro and macrovascular complications in type 2 diabetes.
Glutamine and EGCG are relatively low cost supplements with no reported side effects in the dosages used. The expected short term results of this study are lower lower circulating markers of inflammatory and oxidative stress, and lower markers for procoagulant state. These improvements will eventually result in less endothelial damage with reduced micro and macrovascular complications in type 2 diabetes patients providing a better and more cost effective improvement in quality of life.
If results are promising a longer intervention study is needed to study the

effects on micro- and macrovscular complications in patients with diabetes type 2.

## Study objective

In this pilot study, the objective is to show an improvement in glucose tolerance,a decrease in parameters for inflammation, oxidative stress and a procoagulant state after 4 weeks of daily supplementation of L -glutamine and Epigallocatechin-3-gallate.
Apart from chosen parameters a BIA will be performed at start, after 2 weeks and after 4 weeks of supplementation.
The conditionally essential amino acid glutamine was chosen because:
- it induces insulin production by stimulating the release of glucagon like peptide -1 by jejunal cells
- in beta cells it is recognized as an important signaling molecule in the production of insulin.
- it reduces insulin resistance and improves postprandial glucose tolerance in type 2 DM.
- it is a preferred oxidative fuel for gut epithelial and immune cells.
- it is a precursor for glutathion, arginine, HSP's and PPAR gamma.
-- it reduces the proinflammatiry cytokine response by inhibiting the activation of NFkB.
EGCG is chosen because it is an exogenous, ant-ioxidative phyto-polyphenol that
- inhibits amyloid deposition pancreatic isle cells.
- regulates glucose homeostasis by supporting GLUT 4 translocation in skeletal muscle
- suppresses gluconeogenesis in the liver
- at the level of the gut acts as an antioxidant and antibacterial agent inhibiting carbohydrate splitting enzymes
- after bacterial fermentation in the gut modulates protein kinase and lipid kinase signalling pathways (PI 3-kinase, Akt/PKB, PKC en MAP kinase) beinvloedt
- modulates NFkB activation by downregulation of gene expression.

The effect of both supplements will be assessed by the following parameters
1 Insulin sensitivity, by using an OGTT
2 Inflammatory parameters (CRP, IL-6, IL-18, TNF-*, leucocyte NFkappaB, IL-4, IL-10). IL-6 en TNF-* na vol bloed LPS stimulatie.
3 Oxidatieve stress parameters(Malondialdehyde, TBARS, 8-iso-prostaglandin F2*).
4 Endothelial dysfunction parameters (VCAM-1, E-selectin, ICAM-1, vWF, cGMP, nitrate/nitrite).
5 Pro-coagulant state (PAI-1, fibrinogen, P-selectin)
6 Body composition (BIA).
7 weight changes

## Study design

The association of general practitioners (HONK) has a large population of newly diagnosed type 2 diabetic patients who will meet the inclusion criteria and who will want to participate in the study (based on expert opinion). The study will be performed independently from the producer of the product 2-Prepare® GLNP Life Sciences. The study will be coordinated by a research fellow in a PhD program.
Design
The study is a prospective, open label, randomised, single-center, pilot, intervention study on the effects of glutamine and EGCG in newly diagnosed DMT2 patients.
The duration of the study is 4 weeks of supplementation. At start, after 2 weeks and after 4 weeks a blood sample (20 ml) will be drawn, an oral glucose tolerance test (OGTT) will be taken together with a BIA.

**Intervention**

During the study no change in lifestyle will be advised. Each arm contains 30 patients who will receive for 4 weeks; Control (group1), L-glutamine 0.3-0.5 g/kg/day (group 2), EGCG 3 x 150mg/day or no intervention (group 3) and L-glutamine/EGCG (group 4). Both L-glutamine and EGCG are produced according GMP quidelines. analysed in a ISO certified pharmacy and packed according to HACCP.
L -glutamine is a 9 g sachet protected by light and moisture by a aluminum cover.
EGCG is packed in a capsule of 150 mg (Vcap) contained in a aluminum cover.

**Study burden and risks**

During this 4 weeks study patients have to visit the research department 3 times. At these points the blood samples (20ml) will be taken an OGTT will be performed with a BIA. A BIA takes about 10 minutes. An OGTT takes about 300 minutes

# 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

Patients with newly diagnosed type 2 diabetes mellitus
Ages eligible for study 30 - 80 years old
Genders eligible for study both gender
postabsorptive glucose two times >7 mmoll/L,
BMI <35kg/M2

## Exclusion criteria

Post absorptive glucose * 15mmol/l
Post absorptive glucose * 10 mmol/l and hyperglycemic complaints (polydipsia, polyuria and loss of weight more than 10% in the last month)
Creatinine clearance of < 30ml/min.
Liver tests (ALAT,ASAT) > 3 times the upper level of normal
Patients known to suffer from any malignancy, an acute illness, life threatening disease, or chronic inflammatory condition at the start of the study.
Use of corticosteroids or other anti-inflammatory medication
Preexisting cardiovascular diseases or atherosclerotic diseases.
Pregnancy/breast feeding

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Prevention

## Recruitment

NL

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| Recruitment status: | Will not start |
| Enrollment: | 30 |
| Type: | Anticipated |

# Ethics review

Not approved

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| Date: | 10-08-2012 |
| Application type: | First submission |
| Review commission: | METC Noord-Holland (Alkmaar) |

# 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 |
| --- | --- |
| EudraCT | EUCTR2011-003503-38-NL |
| CCMO | NL37176.094.11 |