Interaction between intestine and osteoarthritis of the hand and the effect of Sustained Release Calcium Butyrate

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This proof of concept study is to estimate the effect of SRCaBu (600 mg daily for four weeks) on compositional and functional characteristics of the microbiome for future sample size calculation.The secondary objectives: 1) To evaluate the short-...

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

Summary

ID

NL-OMON55339

Source
ToetsingOnline

Brief title
Intestine, microbiome and osteoarthritis

Condition

- Joint disorders

Synonym
osteoartritis of the hand

Research involving
Human

Sponsors and support

Primary sponsor: BirrBeheer B.V.
Source(s) of monetary or material Support: Sponsor: BirrBeheer B.V.

Intervention

Keyword: butyrate, low chronic systemic inflammation, microbiome, osteoarthitis

Outcome measures

Primary outcome

compositional and functional characteristics of the microbiome.

Secondary outcome

change in intestinal barrier function, change in systemic inflammation

parameters, immune tolerance and inflammatory response, tender joint count,

pain, functioning of hands, patient*s global assessment, quality of life, stool

behaviour.

Study description

Background summary

Chronic inflammatory diseases are often associated with impaired barrier function of the intestine (*leaky gut*), with dysbiosis of the intestinal microbiome, with impaired intestinal associated immune tolerance and with low, but elevated chronic systemic inflammation(2016 Thaiss Zmora). The association between impaired intestinal barrier function and OA have been described in various studies and it was postulated that amelioration of the impaired barrier function would ameliorate OA (2012 Metcalfe Harte, 2016 Huang Kraus, 2017 Huang Stabler, 2018 Huang Perry). Dysbiosis of the intestinal microbiome is also associated with OA (2018 Biver Berenbaum). Boer et al (2019) demonstrated very clearly that the microbiome of patients with OA of the knee was dysbiotic, as it was marked by an overrepresentation of Streptococcus spp. (2019 Boer Radjabzadeh).
The intestine associated immune system is essential for immune tolerance. A part of this system is the balance between T helper cells (like Th17) and T regulatory cells (Treg). Dysbiosis causes a shift towards T helper cells contributing to low chronic systemic inflammation and impaired immune tolerance (2016 Li Wan, 2017 Omenetti Pizarro).

An important question is the one about causality. Will it be possible to ameliorate chronic inflammatory diseases by treating the deviant functioning of

the intestine? Or is the impaired functioning of the intestine a consequence of the disease? Or has each chronic inflammatory disease with an intestinal component its own specific causality?
Various experimental and clinical studies demonstrated that amelioration / improving of the various functions of the intestine also ameliorate/affect chronic inflammatory diseases. Treatment with dietary fibres resulted in restoration of a balanced microbiome and amelioration of OA in a murine model (2018 Schott Farnsworth). Also in a well-designed and well performed clinical study, treatment with probiotics for a period of six months resulted in amelioration of inflammation, pain and function of patients with OA of the knee (2017 Lei Guo).

Short chain fatty acids (SCFAs, mainly acetate, propionate and butyrate) are of major importance In the homeostasis of the intestine. These SCFAs are formed in the intestinal microbiome by fermentation of non-digestible dietary fibres. Besides a major energy supply (10% of the daily need), butyrate has specific and crucial functions. Butyrate is a specific energy source for the colonocytes and the integrity of the colonic epithelium is butyrate dependent. Butyrate is a potent histone acetylase inhibitor and is essential for the prevention of intestinal cancer (2016 Gonçalves Martel). Butyrate has a central role in the functioning and integrity of the barrier of the intestinal epithelial cells, in the synthesis of anti-microbial proteins (AMP and sIgA) and in immune tolerance. AMP and sIgA are two aspects of the indirect effects of butyrate on the composition of the intestinal microbiome. Additionally, butyrate affects the microbiome also directly. It reduces the toxicity of Salmonella enterica by downregulation of pathogenicity Island 1 (2006 Gantois Ducatelle).
Butyrate affects cells of the intestinal epithelium and of the immune cells associated with the intestine by binding on G-Protein coupled Receptors (GPRs, like GPR41, GPR43, GPR109a). Butyrate has also important intracellular effects. It was shown to act as a major histone deacetylase inhibitor (2014 Donahoe Holley, 2018 Yuille Reichart).

Butyrate is transported in and out of cells by various transporters (MCT1, MCT4, SMCT1, BCRP, (2013 Gonsalves Martel)). Butyrate induces also the formation of these transporters (2002 Cuff Lambert). These transporters (like ABCRP2) have a major role in secretion of uric acid into the intestinal lumen (2016 Matsuo Tsunoda). Improvement of intestinal functioning will improve uric acid secretion (2020 Ferrer Picon Dotti). Serum concentrations of uric acid are associated with the severity of OA of the knee (2017 Ma Leung), and it has a direct effect on the inflammasome and pain sensitization (2019 Yoshida Hagiwara). We postulate that the systemic decrease in uric acid (urate) concentration by Sustained Release Calcium Butyrate (SRCaBu) will contribute to less pain in OA patients.

The application of butyrate as medicine has a long history. Initially it was studied as a as anti-cancer agent (1987 Miller Kurshel). However, taken orally it is almost impossible to reach the needed systemic concentrations because the

high first pass effect in the liver; the liver scavenged the butyrate present in the portal blood. Butyrate has a pKa value of 4.8. This means that in the stomach it will become butyric acid and in the acid form it will easily and passively pass the epithelial layers. Also, the quantity of butyrate that will enter the small intestine will be very limited. Therefore, the effect of butyrate will be limited when it is taken orally in an unprotected form. The unprotected form of butyrate is only used as additive in artificial calf milk. The protected forms, sodium or calcium butyrate with a fat coating, are used as feed additive. It is released in the small intestine where it affects epithelial and immune cells, reinforces the immune system (makes poultry and pigs less sensitive to Salmonella infections), improves the intestinal functions and improves reproductive success (See 2018 Moquet Thesis for extensive overview).
If we take the quantities added to pig or chicken feed and we adjust them pro-rata to the energy consumption by humans (2000 Kcal) a daily dose of 600 mg of butyrate will be equivalent to that consumed by chickens and pigs. Several effective clinical studies have been performed with daily doses varying from 237 mg to 2.4 grams of butyrate.

Three randomized placebo control studies in patients with various inflammatory intestinal diseases in which various forms of protected butyrate were used, are known to us (All studies had a positive outcome, i.e. amelioration of the disease, less pain, less obstipation (2000 Vernia Monteleone, 2013 Banasiewicz Krkowicz, 2014 Krokowicz Stojcev).
In addition, Bouter et al (2018 Bouter Bakker) treated obese and lean people with 4 grams Sustained Release Na butyrate for a period of 4 weeks and found that only lean people showed an improved glucose tolerance. In the mentioned studies no unwanted side effects were observed.

The results of the animal and clinical studies indicate that daily doses round 600mg butyrate in sustained release form will be a good starting dose for clinical studies. Additionally, not only the total dose of butyrate given should be taken into account, but also the release rate of butyrate out of the formulation into the lumen of the small intestine. This release rate determines the amount of butyrate locally available in the small intestine and therefore the concentration of butyrate that can affect the microbiome, the intestinal epithelial cells and the immune cells present in the small intestine. The necessary release rate of butyrate was studied in advance using a mathematical model (2020 Korsten). The release rate of the sustained release tablet used in this study is in line with the proposed release rate of the before mentioned study, namely 0.08-0.2 mmol/h. This release rate will make it possible to reach pharmacologically active concentrations in the small intestine, based on in vitro experiments.

We will perform a clinical study in which we will test the effects of 600 mg butyrate in a sustained release tablet (SRCaBu) on three aspects of the functioning of the intestine: composition of the microbiome, barrier function,

and immune tolerance. The study will be performed in patients with OA of the hand. The role of synovial inflammation in the pathophysiology of OA is well recognized, in particular in hand OA. Inflammatory aspects, such as effusion, gray-scale synovitis and power Doppler signal assessed by ultrasonography studies are present in 96-100% of hand OA patients and are associated with pain (Kortekaas 2014; Kortekaas 2010). In the etiology of OA mechanical damage (caused by high body weight) and systemic factors are of importance. According to Visser et al. in patients with hand OA surrogates for systemic processes are the most important risk factors (2015 Visser de Mutsert). These systemic processes are related to functioning of the intestine and the intestinal microbiome. We hypothesise that 600 mg dd SRCaBu will result in positive effects with respect to microbiome, barrier function and immune tolerance.

Study objective

This proof of concept study is to estimate the effect of SRCaBu (600 mg daily for four weeks) on compositional and functional characteristics of the microbiome for future sample size calculation.

The secondary objectives:
1) To evaluate the short-term effects (i.e. 4 weeks) of SRCaBu (600 mg dd) compared with placebo on pain and functioning of the hands in hand OA patients.
2) To evaluate whether SRCaBu (600 mg dd) lowers systemic inflammation in hand OA.
3) To evaluate whether immune tolerance will improve while lowering inflammation by characterizing the phenotype of T-cells and monocytes and determining the response of activated PBMCs of patients before and after intake of 600 mg dd SRCaBu.
4) To examine the preliminary safety profile of (600 mg dd) SRCaBu in patients with hand OA over 4 weeks.
5) To examine the associations between intestine functioning and pain and functioning of the hands in hand OA patients.
6) To examine the effect of SRCaBu intake on stool behaviour.

Study design

proof of concept, randomized, (double-)blinded, placebo-controlled trial design with follow-up of 4 weeks.

Intervention

Sustained Release Calcium Butyrate (600mg/day) for a period of 4 weeks

Study burden and risks

Burden; 2 visits to Sint Maartenskliniek (consultation and physical

examination; blood pressure, blood sampling (2x), faecal sampling (at home 2x)). Online questionnaires (daily, weekly). Daily intake of 4x 150 mg SRCaBu or placebo.

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

osteoarthritis of the hand

Exclusion criteria

other chronic inflammatory diseases

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-05-2022
Enrollment:	33
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sustained release Calcium butyrate
Generic name:	ibidem

Ethics review

Approved WMO Date:	30-11-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-02-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2020-0071-33-NL
CCMO	NL73382.091.21