Changes in taste perception in patients with interstitial lung disease: The need for new diets and food products.

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07/01/2019-30/06/2019
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The research conducted during this thesis period led to two publications:

Self-reported gastrointestinal side effects of anti-fibrotic drugs in 176 Dutch idiopathic pulmonary fibrosis patients.
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(submitted for publication to lung)

Self-reported gastrointestinal side effects of pharmacotherapy in sarcoidosis patients
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(in preparation)

Acknowledgements

First of all I would like to thank my supervisor prof. dr. A. Bast who has been a great support during the thesis period. He steered me in the right direction whenever I ran into trouble and was always eager to discuss questions and new findings of the research.
He always provide very helpful feedback and helped me to further develop my writing and research skills.

Furthermore I would like to thank M. Drent for the datasets used in both the thesis and the publications. She greatly contributed to both publications and provided very helpful feedback in order to make both studies a success

I would also like to thank, M. Elfferich, P.A.H.M., Wijnen, N.T. Jessurun, Lewis, E. Nancy, and S. de Jong who also greatly contributed in both publications either by developing the survey or by helping during the writing process and data collection.

Finally I would like to thank dr. R. Havermans in advance for examining my thesis and providing further feedback.

Executive summary

Introduction: Interstitial lung diseases (ILDs) are a group of lung diseases affecting the interstitium. Our current knowledge on ILDs is rather limited. Approximately 65% is idiopathic and the two most prevalent ILDs, sarcoidosis and fibrosis, lack effective curative treatment. Current treatment consists of drugs to slow down disease progression or decrease inflammation. Because further support for the patients is required, this research will focus on the possibilities to integrate dietary interventions in the treatment of interstitial lung diseases.

Method: In order to develop a dietary intervention, first the effect of ILDs on taste perception was measured. This was done by analyzing 2 datasets on the burden of IPF and sarcoidosis treatment obtained from the ILD care foundation. Then a narrative review was conducted using the databases PubMed, google scholar and Medline. During this review, food components with beneficial properties for ILD patients were analyzed. Based on the results of both the review and the dataset analyses a food product and a diet plan were developed adapted to the needs of sarcoidosis and fibrosis patients.

Results: Alterations in taste perception were found in 31% of the IPF patients and in 37% of the sarcoidosis patients. The tastes that were affected differed from case to case in both diseases. Because of this, it was not possible to develop one food product adapted to the taste of all patients.

When looking specifically at the food components, the review showed that Vitamin D plays a vital role in lung health and can act as a preventive agent for ILDs. However when used in a therapeutic way it has prosenescent properties in fibrosis patients and could lead to hypercalcemia or hypercalciuria in sarcoidosis. Maintenance of proper vitamin D levels would still be useful for patients, but possible negative effects when used in excess should be taken into consideration. Vitamin K while not being extensively studied is also likely to be beneficial considering its anticoagulant properties, its curative role in other lung diseases like DAH (Diffuse alveolar haemorrhage) and the relation between vitamin K and lung health.

Furthermore did multiple polyphenols like quercetin, resveratrol and curcumin show to be beneficial in lung fibrosis, alleviating the disease due to the anti-inflammatory, anti-fibrotic and anti-oxidant properties. Same was also found for omega-3 fatty acids and melatonin.

In sarcoidosis studies on the influence on dietary components are rather limited, 2 studies on quercetin in human subjects found alleviating effects by a decrease in inflammation and an increase in antioxidant capacity. Melatonin, also tested in one study showed that two years of treatment alleviated sarcoidosis and could reduce ulcers. Furthermore did a previous review of de Boer et al found that inflammatory lung diseases, are alleviated by vitamin E, melatonin, quercetin and EGGC. Therefore the required nutrients for sarcoidosis and fibrosis are relatively similar and could be summarised in one diet plan.

In order to apply this in practice a diet plan and a food product with vitamin K, omega 3 fatty acids, multiple polyphenols and melatonin were developed. The diet plan consisted of three meals a day and a snack rich in either vitamin K, E omega 3 fatty acids or polyphenols and could therefore attribute to a decrease in oxidative stress and inflammation and possibly slow down fibrosis progression. The developed food product was a smoothie which contained all the beneficial food components. Smoothies are easily ingestible and useful to counteract weight loss. Therefore they are also recommended by the ATS (American thoracic society) for fibrosis patients. Because taste perception might be altered other possible ingredients are also suggested so patients can adapt it to their preference.

Conclusion: The results of these studies underline the possibilities of a more multidisciplinary approach in ILD treatment. With the rather high burden of these complex diseases and the lack of effective treatment options, lifestyle intervention in the form of beneficial food products and dietary recommendations could give patients extra support by possibly slowing down the disease and improving the quality of life.

Table of contents

Glossary and abbreviations

25OHD: 25-hydroxyvitamin D, a vitamin D pre-hormone
ACE: angiotensin converting enzyme, used as a marker for sarcoidosis severity
AEC-II: alveolar epithelial cells type II
AKT: protein kinase B
AP-1: activator protein 1, transcription factor regulating gene expression
APC: antigen presenting cells
Bcl-2: B-cell lymphoma 2, protein that regulates apoptosis
Calcitriol: active form of vitamin D
Caspase: protease enzymes regulating inflammation and programmed cell death
CAT: catalase, enzyme with antioxidant capabilities
Cathepsin: a protease
Caveolin-1: gene that encodes the scaffolding protein for caveolae plasma
COX: cyclo-oxygenase
CTGF: connective tissue growth factor
CXCLX: chemokine
DAH: diffuse alveolar haemorrhage
DHA: docosahexaenoic acid
DLCO: diffusing capacity of the lungs for carbon monoxide
ECM: extracellular matrix
EMT: epithelial mesenchymal transition, epithelial cells lose cell adhesion and polarity
ERK: extracellular-signal-regulated kinase
Esat-6: a secretory protein and potent T-cell antigen
FGFR: fibroblast growt factor receptors
FN protein: fibronectin
HFL-1: human fetal lung fibroblast 1
IDH2: isocitrate dehydrogenase (NADP) mitochondrial
IRE1α: inositol-requiring enzyme 1
FasL: fas ligand, transmembrane protein of the TNF family
FGF: fibroblast growth factor
FVC: forced vital capacity
GSH: glutathione, antioxidant
GSH-PX: glutathionperoxidase
HLA: human leukocyte antigen
IFN-y: interferon factor-y pro-inflammatory cytokine
IL: interleukin cytokines produced by macrophages and lymphocytes
ILD: interstitial lung disease
IPF: idiopathic pulmonary fibrosis
JNK: c-Jun N-terminal kinase, protein kinase responsive to cytokines
LDH: lactate dehydrogenase
LTC4: leukotriene C4, inflammatory mediators produced by leukocytes
M-tor: mammalian target of rapamycin
MAPK: mitogen-activated protein kinase
MCP-1: monocyte chemoattractant protein-1 ne of the key chemokines that regulate migration and infiltration of monocytes/macrophages.
mKatG: mycobacterium tuberculosis catalase–peroxidase
MMP9: matrix metallopeptidase 9 an enzyme involved in degradation fo ECM

MMPs: matrix metallopeptidases
MPO: myeloperoxidase, peroxidase enzyme
NAG: N-Acetylglutamate
NF-κB: nuclear factor kappa light chain enhancer of activated B cells
NRF2: nuclear factor (erythroid-derived 2) a protein regulating antioxidant protein expression
PAI-1: plasminogen activator inhibitor-1, a serine protease inhibitor
PDGF: platelet-derived growth factor
PDGFR-B: B-type platelet-derived growth factor receptor
PPAR-Y: Peroxisome proliferator-activated receptor gamma a type 2 nuclear receptor
PTH parathyroid hormone
ROS: reactive oxygen species
Sirt-1: sirtuin 1 deacetylates
SOD: superoxide dismutase, antioxidant
SMAD: proteins that are the main signal transducers for recpters of TGF- β
SnoN: regulatory protein
SPHK1: sphingosine kinase 1
SRAGE: soluble receptor of advanced glycation end products
TAK1: transforming growth factor β-activated kinase 1
TβRII: TGF-β type II receptor
TGF-β1: transforming growth factor β1
Th: T-helper cells
Timp-1: TIMP metallopeptidase inhibitor 1
TLR: toll like receptor
TNF-α: tumor necrosis α, inflammatory cytokine
Treg: regulatory t-cell
VEGF: vascular endothelial growth factor
YAP1: yes-associated protein 1: a protein that regulates genes involved in cell proliferation and suppresses apoptic genes.

Abstract
Introduction: Interstitial lung diseases (ILDs) compromise a group of lung diseases affecting the interstitium. Despite the high burden is a lot still unknown about the pathology of most ILDs. Because of this multiple ILDs like IPF and sarcoidosis lack effective treatment. Therefore this research aims to explore the possibilities of dietary interventions in the treatment process, in order to provide extra support for the ILD patients in their complex disease process.
Method: To get a clear view on how to implement nutritional interventions for ILD patients in an effective way, 2 datasets on the influence of IPF on taste perception were analyzed. Furthermore, a narrative review was conducted to analyze possible beneficial nutrients. Finally, a food product and a diet plan to support patients was developed.
Results: Both IPF and sarcoidosis patients reported to suffer from alterations in taste perception. In sarcoidosis this alteration was mediated by medication, in IPF this was not the case. A narrative review found that both IPF and sarcoidosis patients need a diet high in polyphenols, omega 3 fatty acids, melatonin and vitamin K. A diet plan was developed and a smoothie containing all beneficial nutrients was made.
Conclusion: This research underlines the possibilities to support ILD patients in a more multidisciplinary way. Where dietary and lifestyle interventions could play an important role in the treatment process.

1. Introduction

1.1 Interstitial lung diseases

Interstitial lung diseases (ILDs), in the past also known as diffuse parenchymal lung diseases, confer a group of more than 300 heterogenous lung diseases [1].

These diseases are generally characterised by inflammation or fibrosis of the interstitium leading to dyspnoea, impaired gas exchange and restrictive pulmonary functioning [2]. Frequently occurring symptoms are dry cough, malaise and dyspnoea [3]. Even though most ILDs have a similar clinical presentation, the underlying pathophysiology differs significantly. Approximately 65% has an unknown aetiology and are therefore defined as idiopathic. Other ILDs originate mainly from connective tissue diseases or exposure to environmental substances that could be harmful like asbestos or certain drugs [4]. The idiopathic ILDs, for example idiopathic pulmonary fibrosis (IPF), are likely to have a more complex aetiology with genetic factors, like the MUC5B gene, and environmental factors, like smoking, as an underlying cause of the disease [5–7].

1.2 Prevalence

ILDs are complex diseases with overlapping disease patterns, in order to establish the right diagnosis a process of exclusion and intense investigation is required [8]. This is not entirely possible in all cases, therefore it can be hard to come up with exact epidemiological numbers and the results can differ between different studies. To illustrate this, recent research in France estimated the prevalence of ILDs at 97.9/100000 and the incidence at 19.4/100000 per year [9]. Registry studies in Greece on the other hand estimated the prevalence of ILDs on 17.3/100000 with an incidence rate of 4.63/100000 [10].

Several studies show that the most prevalent ILDs are IPF and sarcoidosis [11–13]. According to the British Thoracic Society, sarcoidosis has an estimated incidence of 3-5/100000 [14]. While the incidence of IPF has been estimated around 12/100000 [14]. However, these numbers are also dependent on study choice and diagnostic criteria used.

1.3 Burden

Despite the difficulty to come up with exact numbers, the estimated burden of ILDs is considered to be rather high. The reported death rate is higher than 2.5 per 100000 in the UK

and the Netherlands [11,15]. The hospitalization grade is estimated higher than 40/100000 capita in countries like Norway and Denmark [15].

When looking specifically at sarcoidosis and IPF, 25% of the people suffering from sarcoidosis develop chronic diseases and will therefore create a higher burden with regard to health-care use and morbidity [16]. The mortality rate is rather low with 1-5% of the patients dying from sarcoidosis or complications [17].

IPF on the other hand has both a high burden and high mortality, with a median survival of 3-years and illnesses like depression, sleep apnea, hypertension and cancer as comorbidities [18]. Even though IPF has a rather small prevalence and incidence in comparison to other diseases, it does attribute for 1% of the total mortality in the UK [14].

1.4 IPF

Idiopathic pulmonary fibrosis is a chronic ILD characterised by progressive fibrosing of the lungs [19]. During this process lung tissue with extracellular matrix, altering the original lung structure [19]. While being described as idiopathic, there is nowadays more scientific clarity on the issue. More insight has been acquired on the pathogenesis and drugs that can slow down the disease process have become available.

1.4.1 Pathogenesis

In the past IPF was thought to be an inflammatory disorder that would progress slowly into fibrosis [19,20]. However since anti-inflammatory therapy proved to be unsuccessful, this theory has been rejected. Later research showed that repetitive injuries of alveolar epithelial cells, likely mediated by genetic vulnerability and exposure to environmental factors, triggers a series of events inducing an impaired repair mechanism [21]. This causes a disruption in the epithelial-fibroblast interaction, increased myofibroblast production, excess collagen production and deposition, extracellular matrix (ECM) accumulation, increased epithelial-mesenchymal transition (EMT), epithelial cell apoptosis and remodelling of the interstitium [19,22,23]. Eventually this will lead to IPF and could as well happen without inflammatory cells supporting the process.

To give a clearer view, current studies show that after epithelial cells are affected by micro-injuries, the epithelial and endothelial cells will respond with the release of different

inflammatory mediators, cytokines, and growth factors like transforming growth factor β1 (TGF-β1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), tumour necrosis factor α (TNF-α), triggering a series of events [19,22,24].

One of these events is an inflammatory phase [22]. During this phase leukocyte influx to the affected area is triggered and inflammatory mediators like TNF-α and interleukin-1 (IL-1) will influence the disease by triggering a continuous process of abortive regeneration [22,24].

Meanwhile, due to the continuous injury, the epithelial cells also keep producing multiple profibrotic mediators, like TGF-β1 and PDGF (16,19,21). These mediators will affect the epithelial cells by promoting cell apoptosis, epithelial-mesenchymal transition (EMT) and cell migration. This in turn will keep stimulating the production of more mediators in a positive feedback loop.

Furthermore these profibrotic mediators will cause fibroblast recruitment, proliferation and activation. Under normal conditions these mediators structure and re-establish the normal extracellular matrix after which they would undergo apoptosis [19,25]. However in the case of IPF continuous exposure to these mediators leads to fibroblast proliferation and differentiation in myofibroblast [19,25]. These myofibroblasts form fibroblastic foci, which can be seen as the hallmark of IPF. Furthermore, they resist apoptosis and producie even more ECM and collagen. This will eventually lead to excess collagen and ECM production altering the lung architecture causing fibrosis [19,25].

1.4.2 IPF treatment in the past.

The first international consensus on IPF treatment came in 2000 [26]. After reviewing the studies published before 2000 the experts concluded that no effective remedy for IPF was known. Therefore they came up with the suggestion to use prednisone, azathioprine or cyclophosphamide as a therapy for IPF. This therapy was suggested due to the idea that IPF was an inflammatory disease [19,20]. When it was tested in the PANTHER study, the intervention had to be terminated preliminary, because too many people in the treatment group were dying [27]. In 2011 new guidelines were published, admitting that the previous treatments did not work and that IPF was probably not a simple inflammatory disease [26]. In these guidelines no therapies were recommended, but multiple recommendations on which drugs not to us were stated, even though they were previously suggested to be beneficial.

1.4.3 Current treatment

For a long time a lung transplantation was the only successful treatment for IPF [28]. However with an 89% survival rate 3 months after transplantation and a median survival rate of 5.8 years lung transplantations have a higher mortality rate compared to other organs [29]. Furthermore, the lungs available for transplantation are limited and the mortality rate of IPF patients on the waiting list is higher than 30% [30]. Underlining the need for other treatment options.

Nowadays two anti-fibrotic drugs are available for IPF treatment, viz pirfenidone and nintedanib. Both have proven to slow down the disease and have a conditional recommendation in current international guidelines for IPF treatment [31].

1.4.4 Pirfenidone

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is a drug that showed to be able to inhibit fibrosis progression in multiple organs like the heart, liver and lungs [32,33]. The drug has multiple modes of action and is known to have anti-inflammatory, anti-fibrotic and antioxidant properties. While the exact underlying mechanisms remain to a large extent unknown, the antioxidant properties come forward in the ability of pirfenidone to scavenge hydroxyl radicals and reduce lipid peroxidation [32,33]. The anti-inflammatory properties come from the down-regulation of TNF-α and TNF-β. Finally animal models show that the anti-fibrotic effect is a result of the inhibition of AKT, p38 and Smad3 phosphorylation, caused by TGF-β1 [32,33]. Furthermore, a decreased collagen synthesis, ECM deposition and reduced fibroblast proliferation and myofibroblast formation are seen in patients following pirfenidone therapy.

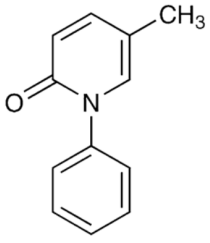


Figure 1: Molecular structure pirfenidone [34]

1.4.5 Nintedinab

Nintedanib originally used as an anti-cancer drug, also showed to be useful in IPF [25]. Nintedanib find its mode of action in its properties as a multiple tyrosine kinase inhibitor, targeting FGF, PDGF and VEGF receptors [25,35]. By competitively binding to adenosine triphosphate binding pocket it inhibits fibroblast proliferation, migration, differentiation and collagen release, countering the IPF process.

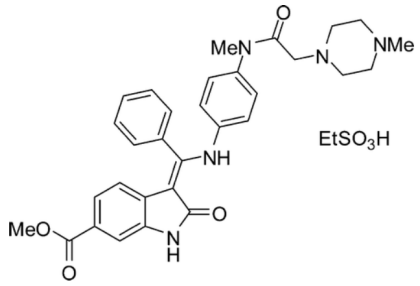


Figure 2: molecular structure nintedanib [36]

1.4.6 Combination

While exact pathways of how nintedanib and pirfenidone work remains to a large extent unknown, does the current scientific data suggest they affect the pathology in a different way. Some studies on the safety of a combination of both showed favourable results [37,38]. The effectivity has not been tested on human subjects but shows promising results in vitro [39].

1.5 Sarcoidosis

Sarcoidosis is an inflammatory disease with an unknown aetiology. current data suggest that the disease is caused by a relation between genetic susceptibility, as seen by the elevated prevalence among people with HLA-DRB1*1101 alleles, and environmental agents [40–42]. This could be infectious organisms and non-infectious environmental agents like metal dust. Implications of sarcoidosis being an autoimmune disease are considered unlikely [43,44].

The disease is recognised by the formation of non-caseating epithelioid granulomas and will resolve after a given time in most cases. It persists in 30% of the cases and is fatal in 1-4% of the cases [45].

1.5.1 Pathogenesis

The disease process of sarcoidosis is likely to begin with an unkown antigen entering the body. This antigen activates type II alveolar epithelial cells (AEC-II), dendritic cells and alveolar macrophages by binding to TLR-2 and possibly ESAT-6 or mKatG receptors [46,47]. Both alveolar macrophages and dendritic cells can phagocyte the antigen and act as antigen presenting cells (APC) by presenting the antigen using their human leukocyte antigen (HLA) class II molecules [46,48].

Among these APC, dendritic cells produce TNF-α, IL-12 and IL-18 once they are activated [49]. Furthermore, they are capable to migrate to the lymph node [46,49]. In the lymph node the dendritic cells will present the antigen to naive T lymphocytes, mainly CD4+ cells, causing T cell polarization and proliferation [44]. This interaction will induce polarization of these naive T-lymphocytes to Th1 and Th17 cells, production of more cytokines and recruitment of inflammatory cells [47,50].

Alveolar macrophages, while also being able to act as APCs, cannot migrate to the lymph nodes [46,51]. Once activated they will secrete multiple cytokines like IL-1 and TNF-α. They also secrete chemokines when stimulated by both TNF-α and IFN-y derived by natural killer cells [46]. This will lead to the attraction of monocytes, Th1, Th17, Treg and B cells.

Finally AEC-II cells influence the pathogenesis by producing more cytokines once activated.

Due to the continuous triggering of the APCs and AEC-II a continuous influx of cytokines will lead to excess recruitment and expansion of lymphocytes.

Th1 cells once activated will express IFN-y. IFN-y on its turn will influence the macrophages by decreasing PPARy expression which decreases IL-10 and increases the expression of TNF-α, matrix metallopeptidases (MMPs) and CXCLX [49]. Due to the decrease in IL-10, myeloid dendritic cells activation is no longer inhibited creating a positive feedback loop. Due to the high levels of TNF-α and IFN-y, and a continuous increase in chemokines more T cells and myeloid cells are attracted supporting the granuloma formation process [49].

Activated Th17 cells produce IL-17A, IL-17F, IFN-Y and IL-22 further stimulating the genesis of the granulomas [52].

The special feature of sarcoidosis granulomas is that the formation happens in an orchestrated matter due to the CD4+ T-cells regulating macrophage activity.

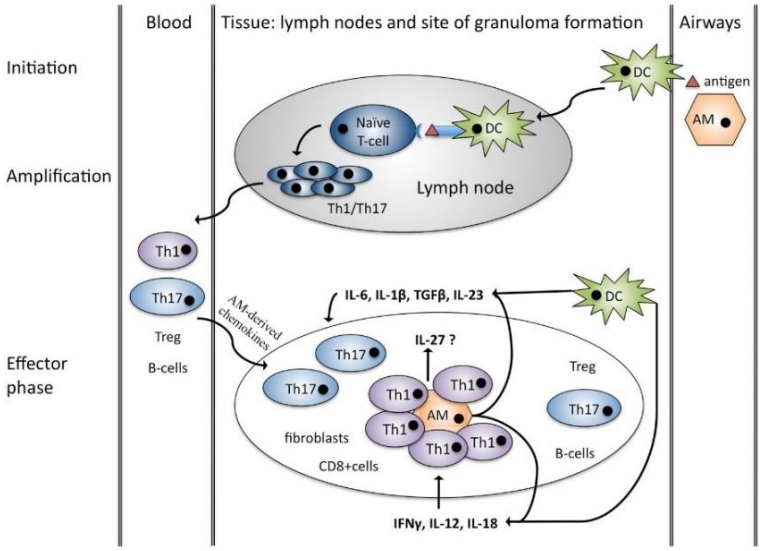


Figure 3: Pathogenesis of sarcoidosis [53]

1.5.2 Resolution

While it's still not entirely clear how the resolution of sarcoidosis is mediated, the current knowledge suggests it happens under the influence of Tregs. The amount of Tregs are normally decreased in sarcoidosis patients, they manifest anti sarcoidotic properties by promoting IL-10, TGF-β and IL-35. IL-10 produced by either Treg, monocytes or macrophages, reduces inflammatory mediators like IFN-y and IL-12. TGF-β while being able to be profibrotic and pro-inflammatory can also inhibit T-cell activation. IL-35 promoted by dendritic and Treg cells is immunosuppressive and possibly influential on Th17 [54]. Another mediator likely to play a role in the resolution of sarcoidosis is IL-27 which stimulates IL-10 and Treg proliferation while inhibiting IL-13 and TNF-α [54].

1.5.3 Corticosteroids

The first line treatment for sarcoidosis consists of corticosteroids, which is mainly used for its anti-inflammatory properties [55,56]. Their effect establishes by restoration of the Th1 and Th2 balance. While also reducing inflammatory mediators, IL-1 and TNF-α, adhesion molecules and receptors [57].

A suggested pathway on a molecular level would be that corticosteroids bind to the cytosolic glucocorticoid receptor, causing a translocation to the nucleus. Here the transcription of genes is either induced or inhibited. An example would be NF-κB, which when inhibited reduces TNF-

α and IL-6 production in macrophages and IFN-y in alveolar T-cells [56,57].

1.5.4 Other drugs

Other drugs frequently used according to the ATS (American thoracic society) are methotrexate which acts by inhibiting folic acid metabolism. It is used as an addition when the response to corticosteroids shows to be inadequate or as a sparring partner to reduce side-effects. Approximately 2/3 of the patients seem to respond to it [56,58].

Azathioprine, hydroxychloroquine, mycophenolate motefil are other drugs used if both methotrexate and corticosteroids do not show to be effective.

Finally when all treatment options are failing, therapeutic monoclonal antibodies infliximab and adalimumab are used [58].

1.6 Potential of dietary interventions

With nowadays more attention going to multidisciplinary treatment approaches, it would be useful to consider diet as an important factor in the treatment of lung diseases. Research continuously showed that dietary factors have a significant influence on pulmonary health [59–61]. When looking at fibrosis for example, recent research found that saturated fat and meat intake increases the risk of developing IPF [62]. While fruit and high anti-oxidant intake show to reduce the chances of developing IPF [63]. Furthermore a previous study also found that inflammation in lung disease could be reduced by certain dietary compounds like omega 3 fatty acids and polyphenols [64].

1.7 Aim

While there have been improvements in the treatment of ILDs, extra support for the patients is needed. The aim of the research therefore is to develop a diet plan and food product specified to the needs and requirements of patients suffering from the ILDs IPF and sarcoidosis.

The research question for this study is: Do changes in taste (dysgeusia/ageusia) occur in patients with interstitial lung disease? Can we, with the obtained knowledge, design new diets or food products that will be acceptable and beneficial for these patients?

In order to answer this research question the following hypothesis will be answered.

Hypothesis 1: patients with interstitial lung disease will experience dysgeusia or ageusia
Hypothesis 2: This change in taste perception is due to the disease and not due to the drugs
Hypothesis 3: based on the results from the research we can develop food products adapted to the needs of patients.

1.8 Experimental approach

In order to answer the first hypothesis, a dataset of 246 patients suffering from IPF and a dataset of 1003 patients suffering sarcoidosis was retrieved from the Antonius Ziekenhuis Nieuwegein. A data analysis will answer whether there is a decreased taste perception and whether this can be attributed to the disease itself or to the drugs the patients are taking.
Based on the result of this analysis and a further literature search, a diet plan and a food product will be developed and tested. This food product will have beneficial nutritional properties and if needed an adapted taste to make it more convenient for patients to use it frequently.

1.9 Relevance

Currently much is still unknown about ILDs, when looking at IPF for example only two drugs have proven to be successful in slowing down the fibrosing process [31]. With growing evidence that the right food components would be beneficial for IPF and sarcoidosis patients. Could the development of adapted diet plans and food products support patients in their complex disease and treatment process. The result of this research could also be used in other ILDs due to the overlapping disease patterns with relation to inflammation, oxidative stress and fibrosis [65].

2. Method

2.1 Study 1: Taste perception in IPF and sarcoidosis

2.1.1 Research design

To answer the first 2 hypotheses a cross-sectional study was conducted. This design was chosen because it makes it possible to show an association between side effects and demographic characteristics in a fast and cost-effective way. In order to do this two datasets regarding the side effects of anti-fibrotic drugs and anti-sarcoidotic drugs were obtained from the ILD care foundation.

2.1.2 The dataset

The dataset for lung fibrosis was acquired in the period between June 2018 and October 2018. The dataset for sarcoidosis was acquired in the period between June 2018 and March 2019
The data was obtained using a questionnaire. First this questionnaire focused on questions regarding the demographic characteristics of the patients, like age and gender. Than questions regarding the drugs they were using and finally a closer look was given to the side effects they were suffering from, for example vomiting or loss of appetite.
The questionnaires were filled in by fibrosis and sarcoidosis patients of the outpatient clinic from the ILD Center of Excellence of the St. Antonius Hospital, by members of the Dutch Pulmonary Fibrosis Patient Society and by sarcoidosis patients of patient associations from the US, the UK and the Netherlands. The questionnaire was anonymous and online, therefore respondents were free to choose where and when they filled it in. In the end 236 patients reacted to the fibrosis questionnaire and 1003 patients reacted to the sarcoidosis questionnaire.

2.1.3 Study population

The study population used in the first analysis consisted of people diagnosed with IPF by a multidisciplinary team in accordance with the national guidelines. Each of them took either no anti-fibrotic drugs, pirfenidone or nintedanib. Since the disease is rather rare patients of all age groups were included. In total 236 respondents filled in the questionnaire. The second dataset analysed consisted of people diagnosed with sarcoidosis by a multidisciplinary team in accordance with the national guidelines. The respondents took either prednison,

methotrexate, azathioprine, Anti-TNF, mycophenolatemotefil or hydroxychloroquine. Also here were all age groups included. The questionnaire was filled in by 1003 respondents.

2.1.4 Eligibility criteria

In order to include the right patients for the research, the dataset was screened with the inclusion and exclusion criteria summed up in table 1.

Table 1: inclusion and exclusion criteria for the influence of ILDs on taste perception.

Inclusion criteria fibrosis	**Inclusion criteria sarcoidosis**
diagnosed by a multidisciplinary team any age group man and women non anti-fibrotic drug users nintedinab users pirfenidone users	diagnosed by a multidisciplinary team any age group man and women non-antisarcoidosis drug users prednisone users methotrexate users anti-TNF users azathioprine users hydroxychloroquine users mycophenolate motefil users
Exclusion criteria IPF	**Exclusion criteria sarcoidosis:**
other pulmonary fibrosis diseases not suffering from IPF people using both pirfenidone and nintedanib missing medical data missing values for taste perception	not suffering from Sarcoidosis missing medical data missing values for taste perception

2.1.5 Screening

The screening procedure is shown in figure 4. 163 IPF patients were included after excluding all non-IPF fibrosis patients, patients with missing medical data and patients with no data on taste perception from the dataset. For sarcoidosis 601 patients were included after excluding patients with missing medical data or missing data on side effects.

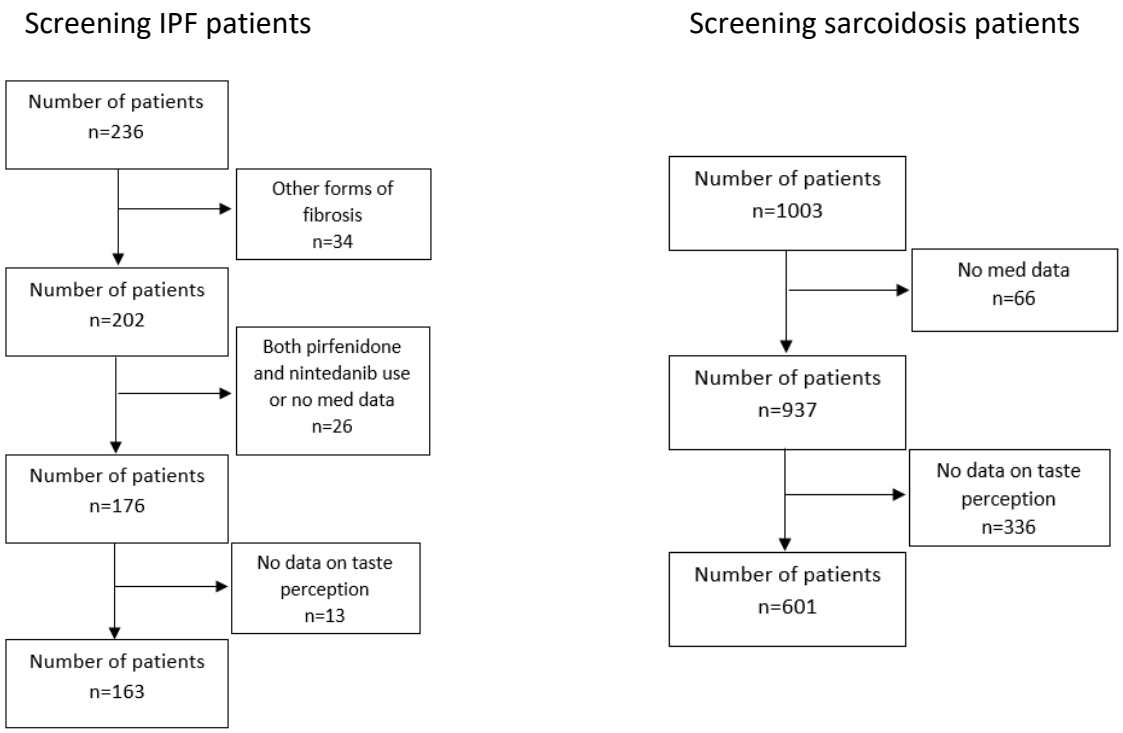


Figure 4: Screening sarcoidosis and fibrosis patients

2.1.6 Measurement

In order to measure whether patients using anti-fibrotic or anti-sarcoidotic drugs would be more likely to report suffering from alterations in taste perception a logistic regression was performed. To prevent bias the most influential covariates were taken into account in the statistical analysis.

2.1.7 Statistical analysis

In order to perform the statistical analysis R 3.5.2 was used [66]. To measure the effect of IPF and sarcoidosis on taste perception a logistic regression with a logic link was performed for both diseases. The response variable consisted in both cases of loss in taste perception, while the explanatory variables were anti-fibrotic drug use, anti-sarcoidotic drug use, sex, age, time since diagnosis, smoking, antacid use, vitamin K use, vitamin D use and multivitamin use. In order to pick the best model, the AIC criterium corrected for small sample size (AICc) was used to select the most important covariates. In order to do so the glmulti-package was used [67]. The model with the highest AIC score was used for the model.

2.2 Study 2: Narrative review:

In order to answer the third hypothesis, a narrative review of the current literature on the influence of dietary components on pulmonary fibrosis or sarcoidosis was performed. This design was chosen in order to give an overview of the current knowledge on a quite broad theme in a fast and cost-efficient way.

2.2.1 Search strategy

In order to gain the required data, the databases google scholar, PubMed and Medline were used. The search terms included diet, nutrition, IPF, pulmonary fibrosis, sarcoidosis, inflammatory lung disease, Vitamin D, 25-dihydroxyvitamin, calcitriol, vitamin K, melatonin, omega 3 fatty acids, lipid mediator, maresin, protectin, polyphenols, flavonoids, curcumin resveratrol and quercetin.

2.2.2 Inclusion and exclusion

We included all types of studies on human subjects and all experimental studies performed either in vivo or in vitro. The studies had to be written in English and target specifically pulmonary fibrosis, sarcoidosis or similar inflammatory lung diseases. Furthermore the study had to test the effect of a certain nutrient or diet on the pathology of IPF, sarcoidosis or similar inflammatory lung diseases.

2. 3 Dietary intervention

Based on the results with regard to taste perception and the conducted review a diet plan and a food product adapted to the needs of ILD patients was developed.

2.3.1 Diet plan

Based on the narrative review a diet plan was developed for both IPF and sarcoidosis patients. This diet plan focused on breakfast, lunch, dinner and snacks for each day of the week. The food products included were rich in beneficial food compounds, consisting either antioxidant, anti-inflammatory or anti-fibrotic properties.

2.3.2 Product development

In order to support the patients a smoothie with all beneficial food components was

developed. The ingredients used in the smoothie are listed in table 1. All ingredients were bought at the “Carrefour Market” in Tongres. The development happened at a kitchen where the different ingredients were combined in a bowl and with the addition of water mixed to a smoothie. The macro nutritional content comes down to 11 grams protein, 79 grams of carbohydrates and 20 grams fat. It is quite a calorie dense in order to support calorie intake in these groups.

Table 2: Ingredients used in the anti-ILD smoothie

Ingredients	Content*	Price (euro)	Price/ kg (euro)
Spinach	10 grams	0.03	3.33
Banana’s	2 (200g)	0.33	1.69
Cranberries	28 grams	0.39	14
Goji berries	28 grams	0.62	22.18
Chiaseeds	14 grams	0.42	30.64
Curcuma	7 grams	0.1	14.18
Coconut oil	14 grams	0.1	6.98
Blueberry	100 grams	1.9 of 0.4	19.92 of 4.38
Total:		3.89 of 2.39	

*The content is aimed to be 0.35 litres approximately

3. Results

3.1 Results study 1: The influence of anti-fibrotic drug on taste perceptions

3.1.1 Demographic characteristics

The data of the 163 IPF and 601 sarcoidosis patients were analyzed and the demographic characteristics are shown in table 3 and 4. Among both disease the percentage of male patients was significantly lower in the non-drug-users group. Furthermore a rather high percentage of people were taking antacids in the IPF group.

Table 3: Summary of the demographic and clinical data of the studied IPF patient sample

	Group I Non-fibrotic drug users	Group 2 pirfenidone	Group 3 nintedanib
Number	18	63	82
Age, years (range)	63 (44) (35-79)	70 (40) (43-83)	68 (34) (46-80)
Gender, male%*	56	82	81
Smoker, yes%	0	3.7	1.6
Time since diagnosis, years	2.7±0.7	2.7±0.7	2.1±0.7
BMI	26.9±3.7	26.6±3.9	26.6±3.6
VitaminD,yes%	56	37	32
VitaminK,yes%	28	17	16
Multivitamin,yes%	17	11	13
Antacid,yes%[a]	77	71	73

Data are expressed in mean ± SD if appropriate.

*p-value < 0.01 group 1 vs 2+3

[a] One missing value

Table 4: Summary of the demographic data of the studied sarcoidosis patient sample

		control	pred	MTX	anti-TNF	Aza	HCQ	MMF
Number		282	416	272	128	53	107	29
Age, years (range)		56 (58) (24-82)	54 (67) (21-88)	54 (59) (22-81)	53 (58) (22-80)	53 (49) (28-77)	52 (49) (23-72)	56 (41) (33-74)
Gender, male%		32,3	37,0	41,5*	35,2	39,6	23,4*	27,6
BMI mean(SD)		28.8±6.0	29.6±7.0	30.1± 6.7	31.3 ±6.9	30.6±6.7	30.5±6.3	29.4 ±5.9
Smoker	yes%	4,7	4,2	4,2	5,6	5,7	3,9	0,0
	In the past%	39,6	33,3	32,5	34,7	37,7	37,3	42,3
	No	55,6	62,4	63,4	59,7	56,6	58,8	57,7
Time since diagnosis	<1 jaar%	9,7	13,5	7,4	0,8	3,8	4,7	3,4
	1-2 jaar%	10,8	12,6	12,6	7,1	13,2	17,8	13,8
	2-5 jaar%	24,7	25,6	33,0	31,0	34,0	26,2	24,1
	>5 jaar%	54,8	48,3	47,0	61,1	49,1	51,4	58,6

Pred= prednisone MTX= methotrexate, aza= Azathiorpine, HCQ = hydroxychloroquine,
MMF = Mycophenolate motefil
Data are expressed in mean ± SD if appropriate
*p-value < 0.01 vs group 1

3.1.2 Statistical outcomes

Table 5 shows the effect of anti-fibrotic drug use on taste perception. After conducting an AICC test, sex and antacid used seemed to be the most influential covariates therefore they were included in the logistic regression.

The table shows no significant difference in taste perception between the drug and non-drug users. Even though in total 31% of all respondents reported to suffer from appetite loss, is this probably not mediated by anti-fibrotic drug use. The included covariates show that antacid use significantly increase loss in taste perception and that men are less prone to loss in taste perception

Table 5: The effect of anti-fibrotic drug on taste perception.

	Estimate	Std E	z-value	Pr(>z)
Intercept	-1.24	0.736	-1.7	0.09
Nintedanib	0.42	0.67	0.63	0.53
Pirfenidone	0.96	0.68	1.41	0.16
Sex	-1.49	0.43	-3.43	p<0.001
Antacid	1.188	0.48	2.48	0.013

Degrees of freedom= 161

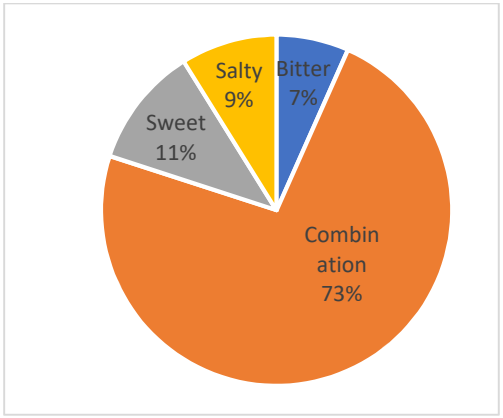
When looking at the data of sarcoidosis 37% of all respondents reported to suffer from changes in taste perception. Table 5 shows the effect of anti-sarcoidotic drugs on taste perception, no extra covariates were taken up. The table shows that alterations in taste perception were mediated by prednisone, azathioprine, hydroxychloroquine and mycophenolate motefil ($p<0.05$).

Table 5: The effect of anti-sarcoidotic drug on taste perception.

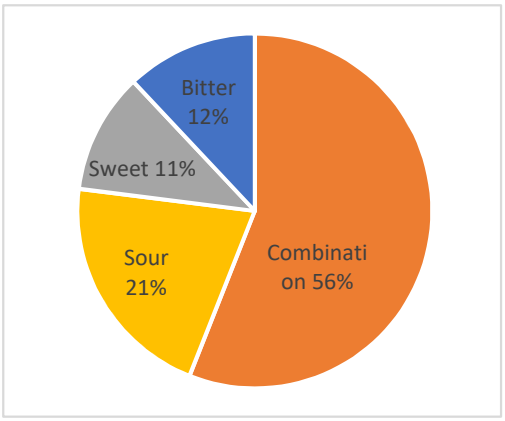
	Estimate	Std E	z-value	Pr(>z)
Intercept	-1.18	0.17	-6.92	p<0.001
Prednsion	0.60	0.18	3.32	p<0.001
MTX	0.28	0.19	1.48	0.14
Anti-TNF	0.15	0.24	0.62	0.535
Azathioprine	0.78	0.35	2.22	0.026
Hydroxychloroquine	0.83	0.25	3.29	p<0.001
Mycophenolate motefil	1.27	0.53	2.40	0.017

Figure 5 shows how the taste perception of the respondents is altered. From the 45 IPF patients who reported to suffer from an altered taste perception 11% states that sweet taste perception is affected, 9% reported an altered salty taste perception and 7% mentioned an altered bitter taste perception. From the 222 sarcoidosis patients 11% reported to suffer from alteration in sweet taste perception, 12% reported an altered bitter taste perception and 21% had an altered sour taste perception. Finally 73% of the IPF patients and 56% of the sarcoidosis

patients mentioned that a combination of tastes is altered, however, this was not further specified in the dataset.



n=45



n= 222

Figure 5: Difference in taste perception

3.2 Study 2: The influence of dietary components on IPF a narrative review.

In order to get a clear view on which food components would be beneficial for IPF patients a narrative review was conducted. During this paragraph the suggested effects that each nutrient might have on IPF are analysed.

3.2.1 Vitamin D

Vitamin D is a steroid hormone mainly obtained via skin to solar UVB exposure. It can however also be acquired via food products like oily fish [68]. While vitamin D is still mainly associated with bone health multiple studies found a relation between vitamin D deficiencies and chronic lung diseases like IPF and other ILDs [69,70]. Therefore it is not surprising that bone fragility and osteoporosis are frequently occurring ILD comorbidities [71–73]. Looking specifically at IPF, a previous study found a higher mortality rate among IPF patients in winter, when there is less sun exposure. Suggesting an effect of vitamin D status on the IPF prognosis [74].

In an experimental setting, a previous in vivo study found that vitamin D deficiency among mice could induce lung fibrosis via activation of the renin-angiotensin system [75].

Possible preventive effects were further confirmed in other in vivo studies with TGF-β1 or bleomycin (BLM) treated mice [76–78]. In these studies vitamin D showed to decrease BLM induced hydroxyproline accumulation and inhibition of myofibroblast proliferation [76,77]. Furthermore vitamin D deficiency also correlated with a lower forced vital capacity (FVC), a

higher diffusing capacity of the lungs for carbon monoxide (DLCO) and higher mortality [76]. Underlying mechanisms of the possible effects are suggested to be due to the inhibitory effect of vitamin D on TGF- β /Smad signalling and due to the inhibition of PI3K/Akt, NF-κB and p38 MAPK expression [76,78].

Two in vitro studies found anti-fibrotic effects in early stage bleomycin exposure and TGF-β1 induced fibrosis, This effect establishes by inhibition of TGF-β1 mediated alteration and expression of EMT transcription factors and ECM gene expression [79,80].

Finally one study consisting of an in vivo and an in vitro experiment when BLM already caused a fibrotic state, found that supplementation of vitamin D has anti-fibrotic effects on myofibroblasts of IPF patients due to inhibition of TGF-β1, Collagen I and III, ACTA2 and VIMENTIN expression [81]. However, the study also reported negative treatment effects of vitamin D. Vitamin D supplementation caused an alteration in the DNA double-Strand break leading to cellular senescence in ATII cells and A549 in vitro cells, worsening the pathology of IPF. Therefore the study advises not to use vitamin D as a treatment [81]. The reason for this rather contradictory results in comparison to other studies is likely because the previous in vivo studies were focused on prevention and pre-treatment rather than on treatment or post-treatment. Furthermore the study reported that this negative effect only occurs when there is both a fibrotic state and vitamin D supplementation, underlining that the negative effect of vitamin D is mediated by the fibrotic state. Therefore it would be reasonable to consider vitamin D as a useful preventive agent, but using it in the treatment could be rather controversial.

3.2.2 Vitamin K

Vitamin K is a vitamin known for its function in blood coagulation and bone homeostasis. The vitamin is mainly present in green leafy vegetables and vegetable oils [82].

Current data suggests that vitamin K has a beneficial effect on people suffering from pulmonary fibrosis for different reasons [83]. First there is data showing an association between IPF and vitamin K deficiency, pointing at vitamin K as a possible nutrient to support people suffering from IPF [84]. Second there is the similarity between IPF and diffuse alveolar haemorrhage (DAH), a lung disease caused by iron accumulation in the lungs leading to oxidative stress and inflammation, which is clearly aggravated by vitamin K deficiency [85,86]. Thirdly even though vitamin K itself has not been tested in vivo or in vitro studies yet, several

studies on vitamin K antagonist have found an aggravating effect on the disease process.

For example a placebo derived controlled double-blind RCT found that high warfarin intake was associated with acceleration in mortality, supporting the importance of the coagulation cascade [87].

A retrospective cohort study showed that anticoagulant therapy leads to faster disease progression and higher mortality [88]. A post hoc analysis showed that IPF patients who underwent anticoagulant therapy had a significantly higher mortality rate (67). The suggested underlying reason for the increased mortality is that anticoagulants have an inhibitory effect on activated protein C worsening the disease [90]. Only one prospective cohort study found a beneficial effect of anticoagulants, with the anti-coagulants and corticosteroids therapy decreasing the mortality rate after acute exacerbation [91]. Due to the majority of data suggesting the negative effects of anticoagulants the ATS expressed a conditional negative recommendation on anticoagulants like warfarin [31]. Therefore it would be reasonable to use vitamin K as a nutrient to counter IPF.

3.2.3 Melatonin

Melatonin is a hormone mainly known for its role in the sleep-wake cycle [24]. It is found in many food sources, however the content varies significantly [92]. Examples of food sources rich in melatonin are nuts and medical herbs. With a recent review underlining possible anti-fibrotic effects of melatonin a closer look will be given to experiments measuring the influence of melatonin on IPF [93].

Several studies conducted on BLM treated mice found a protective effect of melatonin [94–98]. Inflammation neutrophil influx and polymorphonuclear leukocyte accumulation were inhibited and lower levels of TNF-α and IL-1β were noted among melatonin-treated mice [97,98].

Anti-fibrotic effects were established by inhibition of TGF-β1 expression. The suggested underlying mechanism was that melatonin activates the Hippo pathway, leading to inhibition of YAP1, restraining TGF-β1 fibrotic effects as seen by the lower Col1α1 and Col3α1 expression, by less fibroblast proliferation and myofibroblast activation found both in vivo and in vitro [94]. This lower expression of Col1α1 was further confirmed in other studies by a lower grade of collagen 1 deposition in IPF patients [95–97,99].

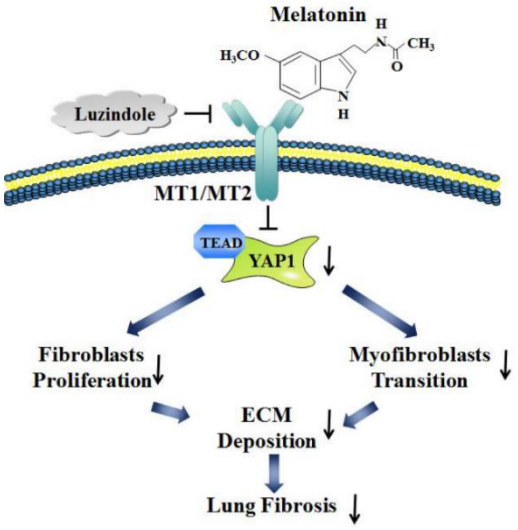


Figure 6: The influence of melatonin on the Hippo/YAP pathway[94].

Another effect of melatonin was established by a reduction in EMT as seen by the lower levels of α-SMA which suggests a lesser increase in myofibroblasts [99,100]. A possible underlying mechanism was the in vitro finding that melatonin mediated the inhibition of Wnt/β-catenin and Smad signalling, therefore decreasing the TGF-β1 induced EMT [100].

Furthermore melatonin did inhibit ER stress and ameliorated the rise in GRP78 and EIF2α which are targets of the ATF6 and PERK pathway respectively. IRE1α phosphorylation was also inhibited restraining the IRE1 pathway and alleviating BLM evoked XP-1 and JNK activation [99].

Further anti-fibrotic effects were established by inhibiting the upregulation of cyclo-oxygenases 2 (COX-2) and edema formation and by inhibiting BLM induced changes in immunoreactivity to nitrotyrosine, poly-ADP- ribose and prevention of further collapsing of alveolar space [95,96,98,99].

Antioxidant properties were established in one study by amelioration of BLM induced alterations in SOD, GSH-PX and CAT activity [95]. While another study found that melatonin was only able to restore normal CAT functioning [97]. Finally increased lipid peroxidation in IPF mice was also inhibited by melatonin treatment [95,97].

In conclusion melatonin did show multiple anti-fibrotic, antioxidant and anti-inflammatory effects, suggesting a beneficial effect on IPF patients.

3.2.4 Omega-3 fatty acids

Omega-3 fatty acids, are essential fatty acid mainly found in fatty fish which are frequently suggested to have a beneficial effect on the immune system [101,102]. There are three types of omega-3 fatty acids α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Pre-treatment with DHA showed to be beneficial in mice [103,104]. From a histological perspective less inflammation, fibrosis and alterations in lung structure were seen [103,104]. Furthermore the mice suffered less from weight loss and had lower mortality.

Anti-inflammatory effects among DHA treated groups were established by the lower levels of dendritic cells and the decrease in neutrophil and lymphocyte infiltration [104]. Also a decrease in the pro-inflammatory cytokines and mediators IL-6, LTB4 and PGE2 were noticed. While normal levels of the anti-inflammatory cytokine IL-10 was restored [104].

Furthermore, DHA established anti-fibrotic effects as seen by the decrease in collagen accumulation and restoration of the lower degree of fibrosis according to the wet to dry weight ratio [103]. One of the suggested underlying pathways was inhibition of TGF-β1 by upregulation of Smad 7 and SnoN [103].

An experiment on perinatal mice showed that DHA supplementation attenuated pulmonary fibrosis, due to less macrophage infiltration, and amelioration of increased MCP-1 expression and sRAGE concentrations. Treatment also showed to increase MMP2 and MMP9 expression. Anti-fibrotic effects were established by inhibition of TGF-β mRNA expression and by attenuation of SMAD2 and SMAD3 phosphorylation showing a decrease in TGF-β signalling. Anti-fibrotic properties were further confirmed histologically as seen by the lower collagen deposition [105].

Another omega-3 fatty acid, γ -linolenic acid also showed to have anti-fibrotic properties. This was established by its ability to reduce collagen deposition and inhibit morphological alterations in vivo. Furthermore it suppressed BLM-induced elevation of leukotriene B4 and increased prostaglandin E1 and 15-hydroxyeicosatrienoic acid which are known to be anti-inflammatory [106]

Finally pre-treatment with flaxseed oil, rich in omega-3 fatty acids, also reduced edema formation and inflammatory cell infiltration [107]. Physiological changes were established by less weight loss, a decrease in vasculitis, decrease in pulmonary lumen patency and reduced septal thickness, [107].

3.2.5 Lipid mediators

With inflammation being an important factor in IPF, is controlling this process essential. One of the actors playing an essential role in acute inflammatory responses are lipid mediators like maresins, protectins and resolvins [108]. These mediators inhibit leukocyte infiltrate and lowers the release of proinflammatory mediators [108].

When looking specifically at IPF, resolvin showed to have multiple anti-inflammatory and anti-fibrotic properties. One In vivo study with mice found that 17(R)-resolvin D1 injection as pre-treatment reduced neutrophil and macrophage infiltration in the lung. Also an attenuation of NF-κB activation and IL-1β was noted. Furthermore resolvin restored MMP9 mRNA and Timp-1 expression. Anti-fibrotic properties were established by reduction of fibrotic mediators TGF-β1 and connective tissue growth factor (CTGF) and by decreased type 1 collagen expression and deposition, suggesting even curative properties [109]. These effects were confirmed via a histological analysis among the resolvin D1 treated mice.

The same study was conducted using resolvin D1 as post-treatment when fibrosis was already settled. This showed quite similar results with less ECM accumulation, reduction in hydroxyproline, an increase in MMP9 gene expression and restoration of Timp-1 expression and inflammation. Only type 1 collagen mRNA remained constant in the experiment [109].

Protectin also showed to be effective in the post-treatment of fibrosis as seen by the decrease in mortality rates and weight loss. Protectin showed to inhibit inflammation by reducing inflammatory cell infiltration and inflammatory cytokine expression, as seen by the reduced IL-1β, IL-17 and TNF-α content [110].

Second protectin showed to be anti-fibrotic by reducing collagen deposition and EMT as seen by the decrease in α -SMA, fibronectin and N-cadherin. While E-cadherin levels increased TGF-β levels decreased both in vivo and in vitro under protectin exposure. Finally lung functioning was improved as seen by the improved blood-gas exchange due to the increased PaO2 and SaO2 content [110].

3.2.6 Polyphenols

Other food derived components showing positive effects on lung functioning are polyphenols [111]. As mentioned in appendix 1 multiple polyphenols have been tested on their influence on pulmonary fibrosis (appendix 1). Among these the most studied in relation to pulmonary fibrosis are curcumin, resveratrol and quercetin.

Curcumin

Curcumin is a flavonoid of which beneficial properties have been suggested. Previous data found anti-inflammatory, anti-fibrotic and antioxidant properties while increasing survival rate [112].

Pre-treatment with curcumin in vivo showed anti-inflammatory properties among mice, dependent on the dose and bioavailability. Two studies found a decrease in macrophage infiltration at a dose of 200mg curcumin [113,114]. No effect with regard to this issue was found in another study using a 5% curcumin diet [112]. Furthermore curcumin caused a decrease in inflammatory mediators as seen by the decreased IL-1β, histamine, TNF-α, TNFR1, NF-κB and COX-2 [112,115,116]. Curcumin did not seem to have an effect on TNFR2 [116].

Anti-fibrotic effects were also established in three studies, which showed a decrease in TGF-β1 expression [113,114,116]. One study however did not find a significant difference in TGF-β1 [115].

In the experiments where the curcumin content was about 5% of the diet or 200mg/kg body weight a decreased collagen, c-jun deposition and hydroxyproline content was noted [112–114]. The suggested cause is inhibition of collagen gene expression and collagen deposition due to lower TGF-β1 and CTGF expression [115,116]. Furthermore LTC4, protein levels, edema formation, N-Acetylglucosaminidase (NAG) activity, LDH content and cell count also decreased by curcumin in 2 studies [114,115].

Both in vivo and in vitro, curcumin established antioxidant properties, by reducing oxidative stress, restoring normal NO levels and MPO activity, and normalising MDA and GSH levels [112,114,115].

One in vivo study on rats found that oral curcumin administration (300mg/kg) as pre-treatment had no effect on rats with regard to anti-inflammatory, anti-fibrotic or mortality reducing properties. If however the curcumin was administered intraperitoneally, similar

beneficial results were found as in previous studies [117]. A possible explanation would be that oral injection of curcumin has a low bioavailability, furthermore is the bioavailability of curcumin in rats also low compared to humans [117]. Another study underlines this bioavailability issue by noting that oral supplementation was less effective than inhaling large porous microparticles (LPMPs) [113].

In vitro studies also showed beneficial effects of curcumin treatment, both pretreatment and post-treatment showed to inhibit TGF-β and TGF-β2 levels and expression, with pre-treatment being more effective. The effect on TGF-β1 was further noticed due to the decrease in TGF-β induced collagen production and deposition, PAI-1 and FN protein production and myofibroblast differentiation [117–121]. Also human fetal lung fibroblast 1 (HFL-1) migration and proliferation was inhibited.

Further anti-fibrotic effects were established by the ability of curcumin to inhibit Smad 1/2, ERK 1/2 Smad 2/3 at a high enough dose [117,121]. Underlying mechanisms for the anti-fibrotic properties are through down-regulation of TβRII expression, and probably through inhibition of the transcription factor c-jun/AP-1 [121]. Also PDGFR-β mRNA expression and upregulation of PPAR-y induced by curcumin decreased [120]

Furthermore, curcumin decreased upregulation of crystatin C and increased PPAR-y expression causing an increased expression of cathepsins B, K and L restoring the cathepsin/cystatin balance [118,119].

Finally an increase in caspase 3 expression and Bax/Bcl-2 was noted in bleomycin HFL-1 cells increasing apoptosis rates. In conclusion does curcumin show to have multiple anti-fibrotic, anti-inflammatory and antioxidant properties, however the required content and bioavailability should be considered.

Resveratrol

Resveratrol (3, 4', 5 trihydroxystilbene) is a stilbene present in grapes, berries and peanuts (103). It has antioxidant and anti-inflammatory properties. Furthermore resveratrol has the ability to modulate lipid metabolism and inhibit platelet aggregation [122].

In vitro studies found that resveratrol was unsuccessful in countering fibroblast proliferation or apoptosis, but had properties to reverse myofibroblast phenoconversion (99). Further anti-

fibrotic effects of Resveratrol were noticed by inhibition of TGF-β mediated cell proliferation and differentiation in lung fibroblasts [124,125]. The underlying mechanisms suggested were inhibition of TGF-β induced phosphorylation of ERK1/2 and Akt, a decrease in phosphatase and tensin homolog restoration (PTEN) expression and inhibition of paraquat-induced oxidative stress related to the NRF2 pathway [124,125].

In vivo pre-treatment with resveratrol showed to inhibit BLM induced fibrosis, weight loss and mortality among treated mice. Antioxidant properties established by restoring malondialdehyde and reduction of ROS while restoring GSH levels [126]. Anti-inflammatory effects caused less neutrophil influx as seen by the MPO activity and reduction of inflammatory mediators, TNF-α, IL-1β, IL-6 and TGF-β [126].

Furthermore resveratrol restored normal Sirt 1 expression resulting in downregulation of inflammation due to inhibition of NF-κB and TGF-β/mTOR signalling [127,128]. The decrease in TGF-β1 signalling also resulted in attenuation of TGF-β1 mediated fibroblast differentiation. Inhibition of EMT was noted and resveratrol restored normal E-Cadherin levels [127].

Another in vivo study showed resveratrol constitutes anti-fibrotic properties by promoting SOD2 and IDH2 deacetylation, restoring cellular homeostasis and inhibiting myofibroblast differentiation [129]. Multiple studies also show a decrease in type 1 collagen deposition [126,127,130].

Underlying anti-fibrotic mechanisms in vivo are suggested by the possible influence of resveratrol on the expression of sirt 1, sirt 2 and sirt 3. It can ameliorate the BLM-induced Sirt 1 expression or increase sirt 3 expression decreasing the susceptibility for fibrosis [127–129,131]. Another suggestion is that resveratrol inhibits Tak1 leading to an anti-fibrotic effect [132]. Finally a study of Impellizzeri et al suggested downregulation of COX-2, reduction of NF-κB p65 translocation and extracellular signal-regulated kinase phosphorylated expression as the mechanism behind the anti-fibrotic effect of quercetin and Resveratrol supplementation [138].

Post-treatment of resveratrol in vivo showed to be anti-inflammatory as measured by the decreased cell count, and the decreased percentage neutrophils to lymphocytes and macrophages [139]. A decrease in inflammatory cytokines TNF-α, TGF-β, IL-1β, and IL-6 was also noted. Furthermore resveratrol showed to have antioxidant properties by reducing lipid peroxidation as seen by the MDA content [130,134]. And histopathological alterations were

reversed. Anti-fibrotic effects were further confirmed by a reduced fibrosis score and lower hydroxyproline levels [130].

Quercetin

Quercetin is a flavonoid of which multiple beneficial effects are suggested like anti-inflammatory and antioxidant properties [135,136]. It occurs in multiple dietary food products like fruit, tea, wine and vegetables [141].

Furthermore an in vitro study found that TGF-β mediated collagen production in fibroblasts is inhibited by quercetin-induced heme-oxygenase-1. This production of heme-oxygenase-1 is likely to be related to quercetin-induced Nrf2 activation [142].

An in vitro study found that quercetin boosts antioxidant capacity by improving Nrf2 activity Furthermore quercetin reduced inflammatory cytokines IL-8 and TNF-α [143]. These results were also seen ex vivo [143].

In vivo, quercetin showed to have anti-inflammatory properties due to lower septal thickness, lower malondialdehyde levels and less neutrophil, leukocyte and macrophage infiltration among quercetin treated groups [133,139,140]. It also illustrated this by reducing TNF-α, IL-1β and IL-6 levels [146]. Furthermore inflammatory cytokines were suppressed by leukocyte and macrophage infiltration and malondialdehyde levels.

Anti-fibrotic effects were seen by the decrease in protein-bound carbonyls hydroxyproline, MMP-7, TGF-β1 expression and collagen production and deposition [139,141,142]. One study however did not find a significant effect on the hydroxyproline content [99].

Quercetin also inhibited SphK1/SAP in both in vivo and in vitro studies [94].

Finally, quercetin boosted antioxidant functioning by activating Nrf2 and decreasing the production of inflammatory cytokines [148].

Post-treatment with quercetin reversed fibrosis, inhibited weight loss and decreased senescence markers p21 and p19-arf in mice. Furthermore resistance toward apoptosis was inhibited, the underlying reason would be AKT activation and promoting FasL receptor and caveolin-1 expression [144]. Expression of Fas was increased and fibroblast apoptosis by FasL and TRAIL increased. Quercitin also stimulated upregulation of caveolin-1 expression and downregulation AKT activation increasing fibroblast apoptosis and attenuating fibrosis [144].

3.3 Study 2 influence of diet on sarcoidosis

3.3.1 Vitamin D

In contrast to most food components, the influence of vitamin D on sarcoidosis is well studied. The idea of a possible influence of vitamin D already came up in 1939, when a rather high prevalence of hypercalcemia among sarcoidosis patients was found [150]. The possible influence of vitamin D was further confirmed by a previous review that found an increased sarcoidosis risk in winter, in people with darker pigment and among people who live in places with less sun exposure [151]. Another study also reported that chronic sarcoidosis is correlated with vitamin D deficiency and that it could bring sarcoidosis further to stage 2-4 of lung involvements[152].

An explanation of this vitamin D related burden can be found in the altered vitamin D metabolism in sarcoidosis patients [151,154].

As seen in figure 7 we can ingest vitamin D either by diet, supplementation or sun exposure. In the liver both vitamin D2 and vitamin D3 get transformed by 25-hydroxylase to 25-hydroxyvitamin D (25OHD). 25 OHD will under normal conditions be transformed to its active form calcitriol mainly by the kidneys under influence of PTH (parathyroid hormone) and calcium. In sarcoidosis however, under the influence of multiple cytokines, like IFN-γ, mainly released by Th17 and Th1 do macrophages have an increase 25-hydroxyvitamin D 1-α hydroxylase gene expression and block 24-hydroxylase expression [145,148]. Stimulating the transformation to calcitriol [150].

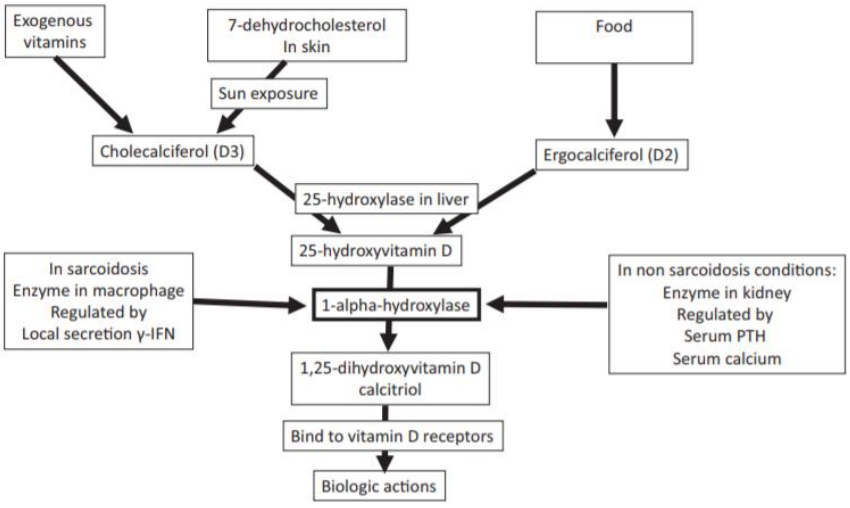


Figure 7: altered vitamin D metabolism in sarcoidosis [150]

This however also means that even though some previous studies found preventive properties of vitamin D, it could have negative effects on the prognosis. Since vitamin D metabolism is altered in sarcoidosis by an increase in calcitriol synthesis, there is an increased risk of hypercalcemia, hypercalciuria and a reduced bone mineral density [145,149,150]. To illustrate this, recent studies found that hypercalcemia and hypercalciuria occur in approximately 5-10% and 30% of the sarcoidosis patients [145,151].

Moreover is there an increased level of VDR (vitamin D receptor) expression in the immune cells [148]. When activated these VDR promote and suppress several products related to bone health like osteocalcin, PTH, calbindin, CYP24A, or CYP27B1. A review from Burke et al. found that increased levels of calcitriol reduce IL-12 levels, antigen uptake by APC, mHC and CD40, CD80/86 expression, T-cell proliferation, IFN-y production, IL-2 production and cellular proliferation [148].

A study of Cappolongo et al showed that vitamin D does not improve the disease pathology unless 25-OHD levels are decreased in the patients [157]. Repletion of 25-OHD is associated with a decrease in calcitriol by suppression of granuloma induced transformation and angiotensin-converting enzyme (ACE) levels and a decrease in serum y-globulins [152]. A decreased chance of hypercalciuria was also found when 25-OHD was repleted [153]. Low 25-OHD levels on the other hand are correlated with higher sarcoidosis activity [154]. Furthermore, repletion of 25-OHD decreases the chance on a reduced bone mineral density. However too much supplementation 25-OHD is again associated with increased chances on hypercalcemia and bone fractures [155]. In sarcoidosis between 10 and 20 ng/ml 25-(OH)D has been associated with the lowest risk on bone fractures.

Therefore we can conclude that it is important to have a balanced level of vitamin D, since a deficiency is related to low calcium absorption, osteoporosis and poorly formed granulomas while an excess can cause too high calcium absorption, hypercalcemia and hypercalciuria [155].

3.3.2 Anti-oxidant food components

Sarcoidosis is associated with an increase in ROS generation and oxidative stress [161]. A previous study found lower antioxidant capacity in sarcoidosis patients as seen by the significantly lower levels of total antioxidant levels measured by the Trolox equivalent, uric acid, glutathione and vitamin C levels. Furthermore were inflammatory cytokines increased among sarcoidosis patients resulting in a significant increased TNF-α/IL-10 and IL-8/IL-10 ratio. Two ex vivo studies showed that quercetin administration improved this state by reducing TNF-α and IL-8 levels [156,157]. The reason for quercetins anti-inflammatory properties besides its anti-oxidant properties, would be the reduction NF-κB modulating TNF-α gene expression. When supplementing quercetin to sarcoidosis patients, total antioxidants levels measured by the Trolox equivalent increased significantly.

Melatonin also showed to be successful in chronic pulmonary sarcoidosis due to its antioxidant properties [163]. One experiment where 18 patients got supplemented with melatonin for two years showed to increase FVC and the DLCO percentage while also normalizing ACE levels. Furthermore skin lesions with lupus pernio disappeared [163].

3.3.3 Anti-inflammatory food components

With sarcoidosis being an inflammatory disease, it is likely that an anti-inflammatory diet could help to suppress the disease process, a review of 162 studies conducted in 2016 by de Boer et al found an effect of different food components on inflammatory lung diseases (appendix 3) [64].

First polyphenols like Epigallocatechin-3-gallate (EGCG), resveratrol, quercetin and flavonoids were found to be anti-inflammatory. A suggested mode of action of these polyphenols is inhibition of NF-κB activation due to the antioxidant properties of EGCG. Furthermore, did EGCG also show to enhance nitric oxide synthases and inhibit collagen production in fibroblast and chemokine expression.

Vitamin E also showed to have anti-inflammatory effects due to its ability to reduce immunoglobulin E levels, COX enzymes and leukotriene synthesis affecting the arachidonic acid metabolism. Other anti-inflammatory effects of vitamin E are upregulation of PPARy, inhibition of lysyl oxidase and protein kinase B, which inhibits NF-κB activation and pro-

inflammatory cytokines production.

Probiotics also showed to be anti-inflammatory. However since probiotics is a broad term comprising multiple bacterial strains of which not all have shown to be anti-inflammatory. Those who do, act via different mechanisms which are currently not known. Therefore the mode of action of probiotics remains uncertain.

Omega 3 fatty acids establish their anti-inflammatory function by competing with omega 6 fatty acids for absorption. With omega 3 fatty acids being anti-inflammatory and omega 6 fatty acids being pro-inflammatory can an increase in omega 3 fatty acids reduce inflammation.

Omega 3 fatty acids activate receptors bound the plasma membrane or in the cytosol like- G-protein coupled receptor, PPAR, transcription factors, establishing its anti-inflammatory effect. It also inhibits LTB4 which promotes inflammatory cytokine production while also inhibiting the generation of IL-1, IL-6 and TNF-α in leukocytes. Finally, it also activates the anti-inflammatory pathways of lipid mediators like resolvins and protectins.

3.4 Diet plan

From the above it can be concluded that both sarcoidosis and fibrosis would have similar dietary requirements. The only difference would be a vitamin E requirement in sarcoidosis and a vitamin K requirement in fibrosis. The need for unsaturated fatty acids, mainly omega 3 fatty acids, melatonin and polyphenols are present in both cases. Because of this our dietary recommendation will be quite similar to the so-called Mediterranean diet which is rich in vegetables, olive oil and polyphenols [164]. In table 5 a diet plan is established for ILD patients, the diet consists of polyphenols due to its high fruit and vegetable content. Furthermore, does it recommend fish 3 times in the week and flaxseed on other days to ensure a high omega 3 fatty acid intake. Melatonin levels are boosted due to tryptophan content in vegetables like spinach, the magnesium in flaxseed and the vitamin B6 in foods like spinach or banana's [160–162]. Direct melatonin is also found in nuts and flaxseed. Finally, the amount of leafy green vegetables is responsible for vitamin K content and can the products high in unsaturated fatty acids like the oils and fish provide the required vitamin E.

Table 5: ILD diet plan

IPF diet	Breakfast	Lunch	Dinner	Snack
Monday	Black tea or green tea rolled oats, blueberries and flaxseed with yoghurt	Whole grain sandwich with roasted vegetables	A glass of Red wine Broccoli sweet potatoes red onion mackerel	Vegetables like carrots or tomatoes fruits like watermelon, grapes, apples, at least 3 servings a day black chocolate
Tuesday	Black tea or green tea Black beans and rice	Toast with avocado, eggs and flaxseed oil	Applesauce tomatoes sweet potatoes poultry	
Wednesday	Black tea or green tea yoghurt with strawberries blueberries and nuts	Roasted vegetables with some turmeric	White beans salmon spinach olive oil	
Thursday	Golden Milk Rolled oats blueberries and flaxseed with yoghurt	Bread with banana and peanut butter	Tomato paste olives whole grain pasta tuna	
Friday	Black tea or green tea Eggs with mushrooms, tomatoes and unions	Vegetable curry soup some slices of bread	Tuna Broccoli mushrooms potatoes	
Saturday	Black tea or green tea bread and hummus and tomatoes	Bread with banana and peanut butter	Barley courgette paprika poultry	
Sunday	Golden milk green tea Bread with olive oil and eggs	Vegetable soup some slice of bread	Applesauce sweet potatoes poultry	

*golden milk is a mixture of coconut milk, honey and turmeric

3.5 Food product

Based on the results of the narrative review (3.2 and 3.3) a smoothie was developed to support ILD patients (figure 8). This smoothie was rich in vitamin K, due to its banana and spinach content, rich in quercetin and resveratrol because of the cranberries, goji berries and blueberries, contained curcumin by its Curcuma levels and rich in omega 3 fatty acid by its chia seeds [163–166]. Finally the smoothie would improve melatonin production due to the tryptophan in spinach, the magnesium in flaxseed, the vitamin B6 in both banana's and spinach and the direct melatonin levels in flaxseed [160–162].

Figure 8: the developed product

Because the taste perception in IPF might be affected in various ways alternative ingredients are suggested in appendix 4.

4. Discussion

This research investigated the possibilities for implementing dietary interventions in the ILD treatment. First alterations in the taste perception of IPF and sarcoidosis patients were measured. Then a narrative review was conducted in order to analyze which nutrients have beneficial properties for patients suffering from one of these ILDs. In both inflammatory lung diseases and pulmonary fibrosis data showed that a diet high in polyphenols, omega 3 fatty acids and melatonin has beneficial effects with regard to inflammation, oxidative stress and fibrosis. Vitamin K also showed to be beneficial in the case of pulmonary fibrosis. While probiotics and vitamin E established anti-inflammatory effects in inflammatory lung diseases. Finally a beneficial diet plan and a smoothie for ILD patients was developed.

Among the sarcoidosis patients 37% reported suffering from alterations in taste perception. According to our data this effect was mediated by the anti-sarcoidotic drugs prednisone, azathioprine, hydroxychloroquine and mycophenolate motefil. Which taste was altered differed from case to case. Among the pulmonary fibrosis patients 31% of all respondents reported suffering from alteration taste perception. Our data also showed that this effect was not mediated by anti-fibrotic drugs use. Which taste was altered here also differed from case to case. The reason for this alteration in taste perception among IPF patients remains unknown. Covariates can have a certain influence, antacid use for example showed to have a significant influence on taste perception. It is also possible that a decrease in lung function might have an impact. Other lung diseases like COPD and cancer also caused alterations in taste perception independent from treatment [167–170]. A possible explanation would be that lung retention which is decreased among IPF patients causes a decrease in taste perception [171,172]. According to a study of Verhagen retronasal smell perception which depends on lung retention, has an important influence on taste and smell perception is [169]. However further data is required to fully understand the reason behind this alteration in taste perception.

In the second part of the research a review was conducted to get a clear overview of the available data on the influence of dietary components on interstitial lung disease. The nutrients which showed to have beneficial effects in both IPF and sarcoidosis were melatonin,

omega 3 fatty acids and polyphenols like quercetin and resveratrol. It should be noted however that this is mainly based on studies on animal and in vitro studies the effect may therefore differ in humans. It is also important to make a separation between preventive and therapeutic food components. Vitamin D, the first food component analysed for example showed to be protective against both sarcoidosis and fibrosis. However when used in excess therapeutically it could aggravate the situation in both diseases, due to side effects like hypercalcemia, hypercalciuria or cellular senescence. Therefore vitamin D levels of the patient should be taken into consideration before supplementing patients.

Vitamin K is presumably effective in IPF, considering to the disadvantageous effect of anticoagulant therapy and the beneficial effects vitamin K has in DAH, which has many similarities to IPF. Furhtermore the idea of vitamin K being beneficial in IPF is increasingly suggested by various researchers [83,174].

Other food components like melatonin, omega 3 fatty acids lipid mediators and polyphenols like quercetin, EGGC, curcumin and resveratrol showed to be beneficial in both diseases due to antioxidant, anti-inflammatory and anti-fibrotic properties. Quercetin and melatonin both even showed to be beneficial in humans. It should however be taken into consideration that spùe polyphenols especially curcumin in this study, have a rather low bioavailability which could inhibit the possible beneficial effects of the food component.

In the third part of the research the previously obtained data were used to create a diet plan and a food product. For the diet plan a week menu high in food components that showed to be beneficial in the review was created. It is clear that in both sarcoidosis and fibrosis a diet rich in polyphenols, melatonin, vitamin E, vitamin K and omega 3 fatty acids would be beneficial. Therefore, the recommended diet is comparable to Mediterranean diet [164]. This is also in line with previous studies which found a positive effect of the Mediterranean diet on lung functioning and a preventive effect against lung cancer [175–177]. A week menu including food products with all these beneficial nutrients was developed and could therefore be used to support patients.

However it should be noted that the banana apple rice toast (BRAT) diet which is already used in IPF patients suffering from diarrhea as a consequence of nintedinab use is not in line with this diet. Therefore it would advisable to carefully consider which diet would be best applicable to taking the possible side-effects into account or to choose for a combination

between both diets.

Finally a smoothie high in polyphenols, omega 3 fatty acids , vitamin K and vitamin E was developed. Due to the added food components this smoothie should have anti-inflammatory, anti-oxidant and anti-fibrotic properties, and therefore contribute to a healthy diet for IPF and sarcoidosis patients. The smoothie is also likely to be beneficial in other inflammatory lung diseases and possibly also in other ILDs since the pathology of most ILDs is quite similar. Furthermore are smoothies easy to ingest and calorie dense it was, it could also be useful in countering weight loss [175].

Supplementation or diet

When the efficacy of nutrients on disease has been proven, it is important to consider what the best way of administration would be. Most studies conducted were in animal models or in vitro, multiple factors like bioavailability may differ in humans and therefore cause alterations in effect. Some food components and in this case especially polyphenols, have low bioavailability and normal administration via diet could have a too low absorption to cause a significant effect. Furthermore the given amount of food components in experiments is often rather large and not always achievable via normal dietary intake. The question therefore remains whether it would be more beneficial to provide individuals with these specific food components via diets or via supplements. When looking at vitamin K, phylloquinone which is the vitamin K that comes from leafy green vegetables is for 80% absorbed in its free form, in spinach it would only be 4-17% of that amount [176], [177]. However absorption could be increased by consuming it with fat [178]. Vitamin E showed to be absorbed best when it is combined with fat, sufficient amounts of this food component could be taken in by diet [179]. Studies found that quercetin is better absorbed when taken in as a cereal bar rather than as a capsule [183]. Also, the addition of dietary fat or fructo-oligosaccharides and vitamin C status showed to further improve absorption [180]. Resveratrol is one of the polyphenols with the highest absorption with 75% being absorbed. However it has a low bioavailability which can be enhanced either by using naturally occurring resveratrol analogues or by using synthetic derivatives [184,185]. This low bioavailability also poses a problem in other polyphenols like curcumin [183]. EGGC is better absorbed in capsules without food [184]. The bioavailability of omega 3 fatty acids is similar in dietary sources and supplements. Therefore the ADA (American Dietetic Association) recommends intake via diet [185]. So in order to use diet as a

tool in the treatment of ILD it is important to consider how food components could be taken up in the most efficient way.

Limitations

During this study there were also some limitations. First of all alterations in taste perception were self-reported and therefore more vulnerable to bias. Furthermore in the case of IPF it is not entirely possible to establish whether the disease is the exact cause of the altered taste perception. Our data took multiple covariates into account and found that antacid use and sex also have an influence on alterations in taste perceptions. Covariates that were not measured in the questionnaire might also have an influence.

If a person reported that the perception of a combination of tastes was altered, the current dataset did not further specify which tastes were altered. Therefore, it was not possible to adapt the food product to one specific taste which would fit all ILD patients.

For the review a limitation would be that there are rather few studies conducted on humans, therefore it would be possible that some food components are less effective in humans. Also most studies measured preventive effects of food components instead of therapeutic effect.

When it comes to the diet plan and the food development the biggest limitation is that it was not possible to test the efficacy in fibrosis and that the bioavailability is rather hard to estimate. Therefore further research is required to analyse the efficacy of dietary compounds in ILD patients.

Future recommendations.

The current study results underline possible beneficial effects of dietary components on interstitial lung diseases. With limited treatment options and a rather high burden of side effects it would be advisable to act in a multidisciplinary way to counter the disease. The American lung foundation suggests that lifestyle interventions like physical activity, coping with stress and stopping with smoking could improve energy, mood, sleep and quality of life in IPF patients [178]. Furthermore does it suggest treatment with drugs to reduce side effects or slow the disease progression down. Finally with the addition of good nutrition it would be possible to enhance the previously mentioned effects and further improve the quality of life of IPF patients. Therefore a multidisciplinary treatment as suggested in figure 9 could provide patients with extra support in their complex disease process.

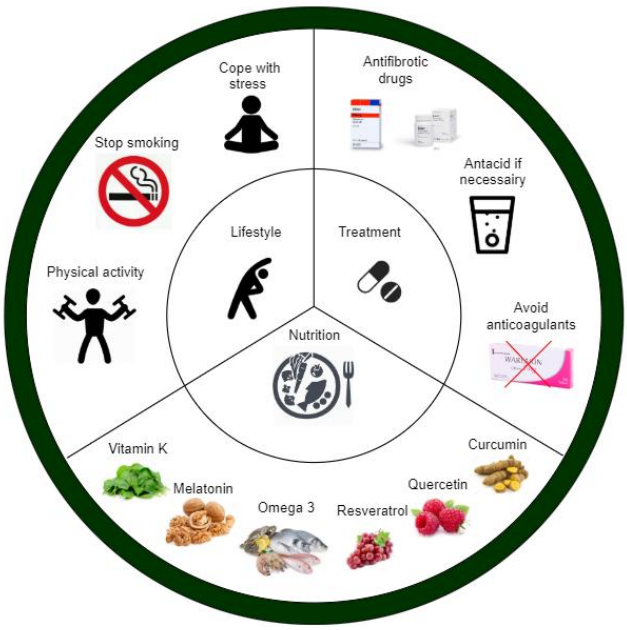


Figure 9: Suggested lifestyle intervention on IPF

The same could also be said about sarcoidosis, while the disease has a significantly lower burden. It can be useful in order to reduce the burden and decrease the chances of sarcoidosis to become chronic. Although studies specifically focussed on the influence of dietary components on sarcoidosis are rather limited, with the current body of knowledge on the influence of diet on inflammatory lung diseases it would be possible to provide patients from the required dietary interventions.

5. Conclusion

Interstitial lung diseases are complex diseases with limited treatment options. This research underlines the possibilities of a more multidisciplinary approach in ILD treatment using both dietary interventions and medical treatment in order to provide the required support.

6. Valorization

By implementing dietary interventions into the treatment of ILDs it would be possible to slow down disease progression, reduce drug requirements and prevent further complications. Therefore the consumer has a higher quality of life, while health care costs are reduced.

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Appendix 1: Summary polyphenols of influence in IPF.

Nutrient	Amount of studies	Suggested anti-fibrotic mechanisms	Source
Rhapontin	1 in vivo and in vitro study	-reduction of LOX 2 and TGF-β1 -increase AMPK expression. - less collagen deposition - Less α-SMA and HIF-1 α expression - Reverse of ECM	[186]
Baicalin	2 in vivo studies	-inhibt p-ERK ½ -TFG-β1 inhibition -heaptic lipid disorder	[187], [188]
Baicalein	1 in vivo study	-P inhibits TGF-β1 and p-smad-2/3by repression of miR-21 levels - decrease in hydroxyproloine and α-SMA -increase in lung index	[192]
Diosmetin	1 in vitro study	- counteracts TGF-β1 induced EMT by inhibiting ROS generation - Inhibition of the PI3K/Akt and MAPK pathways	[190]
Daidzein	1 in vivo study	-Reduce COX2 and NFk-β - Reduces expression of MMP-2 - Increase of TMP1 expression -Regulating apoptosis	[194]
Epigallocatechin	1 in vivo and in vitro study	-Less p-Smad, type collagen and α smooth muscle actin	[192]
Luteolin	1 in vivo and in vitro study	-less E-cadherin -less TGF-β1 -less Smad 3 phosporylation	[193]
Naringenin	1 in vivo study	-downregulates TGF-β -reduction of regulatory t Cells	[194]
Tectorigenin	1 in vitro study	-inhibit fibroblast proliferation -enhances miR-338 expression -less LPA1	[195]

Naringin	1 in vivo study	-reduce TNF-α, TGF-β1, MMP-9 and TIMP-1, and increase antioxidant activities of SOD, GSH-Px and HO-1 -decrease inMDA levels.	[196], [197]
juglanin	1 in vivo study	-lower levels of α-smooth muscle-actin (α-SMA), collagen type I, collagen type III, and transforming growth factor-β1	[198]
apigenin	1 in vivo study	-inhibit cell growth -inhibit TNF-α and TGF-β cytokines -increase in CCN5 expression decrase in CCN2 expression	[199]
Isorhamnetin	1 in vivo and in vitro study	-reduce type-1 collagen and α-SMA expression -reduce EMT and ERS	[200]
Lycopene (carotenoid)	1 in vivo study	-less fibrosis -reduction of TNF- α -less NO -less malondialdehyde. -higher SOD	[201]
Astilbin	1 in vivo and in vitro study	-α-SMA -snail -increase in E-cadherin -increase in SP-C -blocks the hedgehog pathway	[202]
Hydroxysafflor yellow A	2 in vitro 2 in vivo studies	-Decrease in TNF-α, IL-1β, and IL-6 expression -less NF-κB p65 -less TGF-β1, α-SMA, and collagen I -inhibit mad3 phosphorylation -activation of MRC-5 cells	[203]–[205]

Appendix 2: Table on specific food products influencing IPF

Food product	Influential nutrients	studies	Result	
Oil				
Pistacia Lentiscus Oil	Rich in Linoilic acid and palmitic aid	1 in vivo	-decrease in TGF-β -antioxidant -no effect on fibrosis and inflammation lipid per, SOD & CAT	[206], [207]
Fish oil	Essential fatty acids eicosapentaenoic acid	3 in vivo	-less increase in lung protein -less increasehydroxyproline -less inflammation -no preventive properties	[208]–[210]
Planch seed oil		1 in vivo	-regulation of Keap1/Nrf2 -antioxidant	[211]
Flaxseed oil	Long-chain omega-3 fatty acids, α linoleic acid	1 in vivo	-reduced septal thickness -delayed edema formation -inflammatory cell infiltration -reduced pulmonary arterial lumen -decreased septal thickness	[107]
Plant extract				
Phyllanthus Emblica leaves extract	gallic acid, rutin, caffeic acid, kaempferol and other active phytoconstituents.	1 in vitro	-scavenging of NO and lipid peroxidation -increase in GSH, SOD and catalase. -ameliorate CCI4 induced injury -decreases TBARS, H2O2	[212]
Mogroside IIIE		1 in vitro and in vivo	-inhibit collagen deposition -inhibit fibroblast activation -inhibition of TLR4 signals	[213]
Date palm sap		in vivo	-restore normal MDA, SOD and CAT levels -decrease hydroxyproline	[214]
Fruit				

Berberis vulgaris fruit extract		in vivo	-reduction of TNF-α, IL-6 and TGF-β1	[215]
Passion fruit peel extract		in vivo	-less type 1 collagen -less inflammatory cell infiltration -less hydroxyproline deposition	[216]
Tea				
Black tea		in vivo	-decreased expression in α-SMA -down-regulation of TGF- β -upregulation of IFN-γ	[217]
Green tea extract epigallocatechin 3 gallate		in vivo	-reduce collagen depositions, MDA, enhanced SOD, inhibited (myo)fibroblast proliferation, protect (AE2) cells, regulated serum levels of TGF-β1, IL-6, IL-10, and TNF-α. activate Nrf-2 -inhibit weight loss -antioxidant propertie -hydroxyprline	[218], [219]
Green tea extract		in vivo	-less malondialdehyde -endothelin-1 -preproet-1 mRna expression	[220]
Green tea		in vitro in vivo	-scavenge ROS -inhibit neutrophil apoptosis -inhibit neutrophil angiogenesis	[221]

Appendix 3: anti-inflammatory food components.

Food item	Inflammatory effect score	references
Epigallocatechin-3gallate (EGCG)	-1.000	(Chen et al. 2002; Wheeler et al. 2004; Bani et al. 2006; Kim et al. 2006; Qin et al. 2011; Chan et al. 2012; Lee et al. 2013; You et al. 2014)
Vitamin D	-1.000	(Dimeloe et al. 2012; Kuo et al. 2012; Agrawal et al. 2013; Zhong et al. 2013)
Vitamin E	-1.000	(Okamoto et al. 2006; Wagner et al. 2007; Wagner et al. 2008; Wiser et al. 2008; Mabalirajan et al. 2009; Geiser et al. 2013; Hernandez et al. 2013)
Resveratrol	-0.889	(Culpitt 2003; Donnelly et al. 2004; Birrell 2005; Lee et al. 2009; Knobloch et al. 2010)
Quercetin	-0.864	(Donnelly et al. 2004; Boots et al. 2009; Boots et al. 2011; Verma et al. 2013)
N-3 PUFAs	-0.743	(Payan et al. 1986; Arm et al. 1988; Broughton et al. 1997; Hodge et al. 1998; Okamoto et al. 2000; Mickleborough et al. 2003; Matsuyama et al. 2005; Mickleborough et al. 2006; de Batlle et al. 2012; Kunitsugu et al. 2012; Jang et al. 2014; Schuster et al. 2014)
Flavonoids	-0.714	(Park et al. 2007; Geraets et al. 2009; Xie et al. 2009; Wu et al. 2011; Kim et al. 2013)
Fatty acid supplementation	-0.667	(Kanwar et al. 2008; Wood et al. 2010)
Probiotics	-0.538	(Charng et al. 2006; Feleszko et al. 2007; Forsythe et al. 2007; Moreira et al. 2007; Karimi et al. 2009; Lim et al. 2009; Hougee et al. 2010; Lyons et al. 2010; Kukkonen et al. 2011; Jan et al. 2012; MacSharry et al. 2012; Miraglia Del Giudice et al. 2012; Zhang et al. 2012; Harb et al. 2013; Kim et al. 2013)
n-3 + n-6 PUFAs	-0.500	(Surette et al. 2003; Broekhuizen et al. 2005)

Data was retrieved from a previous study from de Boer et al. [64]

Appendix 4: Alternative ingredients for the ILD smoothie

Beneficial food components	used	Alternative 1	Alternative 2
Vitamin K	Spinach Banana	Kale	basil
Quercetin/ Resveratrol	Cranberries Blueberries gojiberries	Grapes Cranberries	Dark chocolate
Curcumin	curcuma	turmeric	
Omega 3	chiaseed	flaxseed	seaweed

[225,226]

Appendix 5: publication 1 self-reported Gastrointestinal Side effects of Anti-fibrotic Drugs

Self-reported Gastrointestinal Side effects of Anti-fibrotic Drugs in Dutch Idiopathic Pulmonary Fibrosis patients

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Keywords
Anti-fibrotic drugs · Idiopathic pulmonary fibrosis · IPF · Nintedanib · Pirfenidone · Side effects · Treatment

Running title Gastrointestinal Side effects of Anti-fibrotic Drugs in IPF

Abstract

Purpose Idiopathic pulmonary fibrosis (IPF) is an inexorably progressive disease, which has a great impact on patients' lives. Pirfenidone and nintedanib are approved and recommended

anti-fibrotic drugs for patients with IPF. The aim of this study was to evaluate self-reported gastrointestinal side effects of anti-fibrotic drugs in 176 Dutch IPF patients**.**

Methods A cross-sectional web-based anonymous survey about complaints and side effects was conducted among IPF patients in the Netherlands. Logistic regression was used to quantify whether pirfenidone and nintedanib caused complaints of nausea, vomiting, diarrhea, appetite loss, weight loss or loss of taste or smell perception.

Results The questionnaire was completed by 176 IPF patients, 71 of whom used pirfenidone and 85 nintedanib, while 20 patients did not use any anti-fibrotic drugs. Nintedanib users reported complaints of diarrhea, vomiting, weight loss, and loss of appetite ($p<0.01$). Nausea was significantly increased ($p<0.05$). Pirfenidone caused increased appetite loss ($p<0.01$) and the risk of weight loss ($p<0.05$). The increasein loss of appetite and weight loss did not differ significantly between the two drugs.

Conclusion The current study showed that nintedanib causes a significant increase in diarrhea, vomiting, weight loss and loss of appetite, while pirfenidone led to loss of appetite. Our results suggests new avenues regarding dietary recommendations for IPF patients.

Word count abstract 207

Word count manuscript 2607

Introduction

Idiopathic pulmonary fibrosis (IPF) is a serious, inexorably progressive disease, which usually affects middle-aged and older adults. While IPF is by definition "idiopathic" (i.e., of unknown cause), the list of potential fibrogenic triggers that have been associated with IPF includes smoking, chronic microaspiration of gastric content and chronic infection. IPF varies from person to person. In some cases, fibrosis develops quickly, while in others, the process is much slower and the disease remains stable for years. It carries a 5-year survival rate of approximately 20%, which is worse than that of several types of cancer [1, 2] . Although IPF is the first or second most commonly encountered form of interstitial lung disease (ILD) (range 17%–86%), its overall incidence and prevalence are unclear. Published incidence rates have ranged from 0.6 to 17.4 per 100,000 person years. To date, there is no cure for IPF. In addition to other care options endorsed by the ATS guidelines, including pulmonary rehabilitation, long-term oxygen therapy, lung transplantation and antacid therapy, new anti-fibrotic drugs have recently become available [3]. Pirfenidone and nintedanib, two compounds with anti-fibrotic properties and pleiotropic mechanisms of action, have consistently proven to be effective in reducing functional decline and disease progression in IPF, and have been approved as standard of care worldwide [3, 4]. Despite substantial differences in the mechanism of action of these two compounds, their treatment effect is strikingly similar, reducing the decline of forced vital capacity (FVC) by approximately 100 mL/year. Individual treatment options should therefore be discussed with each newly diagnosed IPF patient, considering not only the potential benefits but also the side effects, which are not completely identical for these two drugs.

A chronic condition such as IPF may have a substantial impact on patients' quality of life (QoL) [5], and the same is true for the possible side effects of drugs used to treat this progressive disorder. Common side effects of both drugs include nausea, diarrhea, weight loss

and loss of appetite. Pirfenidone is also known to cause changes in taste and smell perception [6], while similar effects have not been reported for nintedanib. These side effects are regularly reported by patients, but relatively little is known about their real prevalence. We therefore studied the self-reported side effects of anti-fibrotic drugs in a Dutch sample of IPF patients.

Materials and methods

Study design

In cooperation with the Dutch Pulmonary Fibrosis Patient Society (Longfibrosepatiëntenvereniging Nederland), the ild care foundation has designed a questionnaire about side effects of anti-fibrotic drugs. This questionnaire includes questions about their disease and any problems these patients may have experienced regarding the use of anti-fibrotic drugs as well as other medication. In addition, it concerns the burden of disease and the symptoms experienced by patients with IPF. Respondents were asked to complete the questionnaire even if they had never experienced any problems with drug use. The questionnaire was used in a cross-sectional web-based anonymous survey, conducted from June 2018 to October 2018 among a sample of IPF patients in the Netherlands.
This study was performed in accordance with the Declaration of Helsinki and its amendments.

Study subjects and procedure

The overall study sample included IPF patients who were known at the outpatient clinic of the ILD Center of Excellence of the St. Antonius Hospital, Nieuwegein, the Netherlands, and/or who were members of the Dutch Pulmonary Fibrosis Patient Society. All subjects had been diagnosed with IPF by a multidisciplinary team according to international guidelines [7]. They were invited to complete the questionnaire by means of an advertisement in the ILD Newsletter of the ILD Center of Excellence at Nieuwegein, while patients visiting the centre's outpatient clinic were also approached. Patients were recruited without incentives, since the survey was anonymous. All patients had sufficient command of the Dutch language and internet access. The survey was developed using the online questionnaire tool *Surveymonkey* (www.surveymonkey.com). The questions concerned the burden of disease and symptoms experienced by the patients with IPF. Further questions concerned demographics (gender, age, duration of IPF), and the use of medication.

Statistical analysis

All statistical analyses were performed using R version 3.5.2, retrieved from the R Foundation for Statistical Computing [8]. To test the adverse effects of pirfenidone and nintedanib, the variables nausea, vomiting, diarrhea, weight loss, appetite loss and loss of taste or smell perception were evaluated using logistic regression analysis with a logit link. Drug use was included as an explanatory variable, with three factors: pirfenidone (n=71), nintedanib (n=85) and non-drug users (n=20). A correlation matrix (appendix 1) was used to select which of the covariates of age, gender, smoking, time since diagnosis, BMI, antacid use, vitamin D, vitamin K and multivitamin supplementation should be included. If any of the covariates correlated with any of the adverse side effects at a significance level p<0.05 or lower, it was included in the final model.

Results

Table 1 shows demographic and clinical data from 176 Dutch patients suffering from IPF, 20 of whom did not use any anti-fibrotic drugs (Group 1). Pirfenidone was used by 71 patients (Group 2) and 85 patients used nintedanib (Group 3). The non-drug users (Group 1) included significantly fewer men ($p < 0.01$) than the drug users (Groups 2 and 3). Other factors did not differ significantly between these groups (Table 1).

Table 1 Summary of the demographic and clinical data of the three idiopathic pulmonary fibrosis (IPF) patient groups

	Group 1 Non-drug users	Group 2 Pirfenidone users	Group 3 Nintedanib users
Number	20	71	85
Age, (range, min-max), years	63 (35-79)	70 (43-83)	68 (46-80)
Gender, male %	55*	81.7	78.8
Smoker, yes %	0	1.4	3.5
Time since diagnosis, years	2.7±0.7	2.7±0.7	2.1±0.7
Having used medication longer than 12 months %	NA	68.1	56.6
Oxygen use, %	31.6	45.5	45.1
BMI (kg/m²)	27.2±3.6	26.4±3.6	26.6±3.8
Vitamin D, yes %	50	32.4	37.6
Vitamin K, yes %	25	15.5	18.8
Multivitamin, yes %	15	11.1	11.8
Antacid, yes%	78.9	73.2	71.8

Data are expressed as mean ± SD or percentage if appropriate.
BMI=body mass index. NA=not applicable
*p-value < 0.01 group 1 vs 2+3

Figure 1 shows the side effects among the three IPF patients groups.

Nintedanib users reported significantly more diarrhea and weight loss than Group 1. Because none of the respondents in Group 1 reported vomiting, it was not possible to statistically test for a direct effect. However, there was a significant difference between pirfenidone and nintedanib users in the incidence of vomiting, which was higher among nintedanib users. Pirfenidone users were more likely to suffer weight loss than subjects in Group 1.

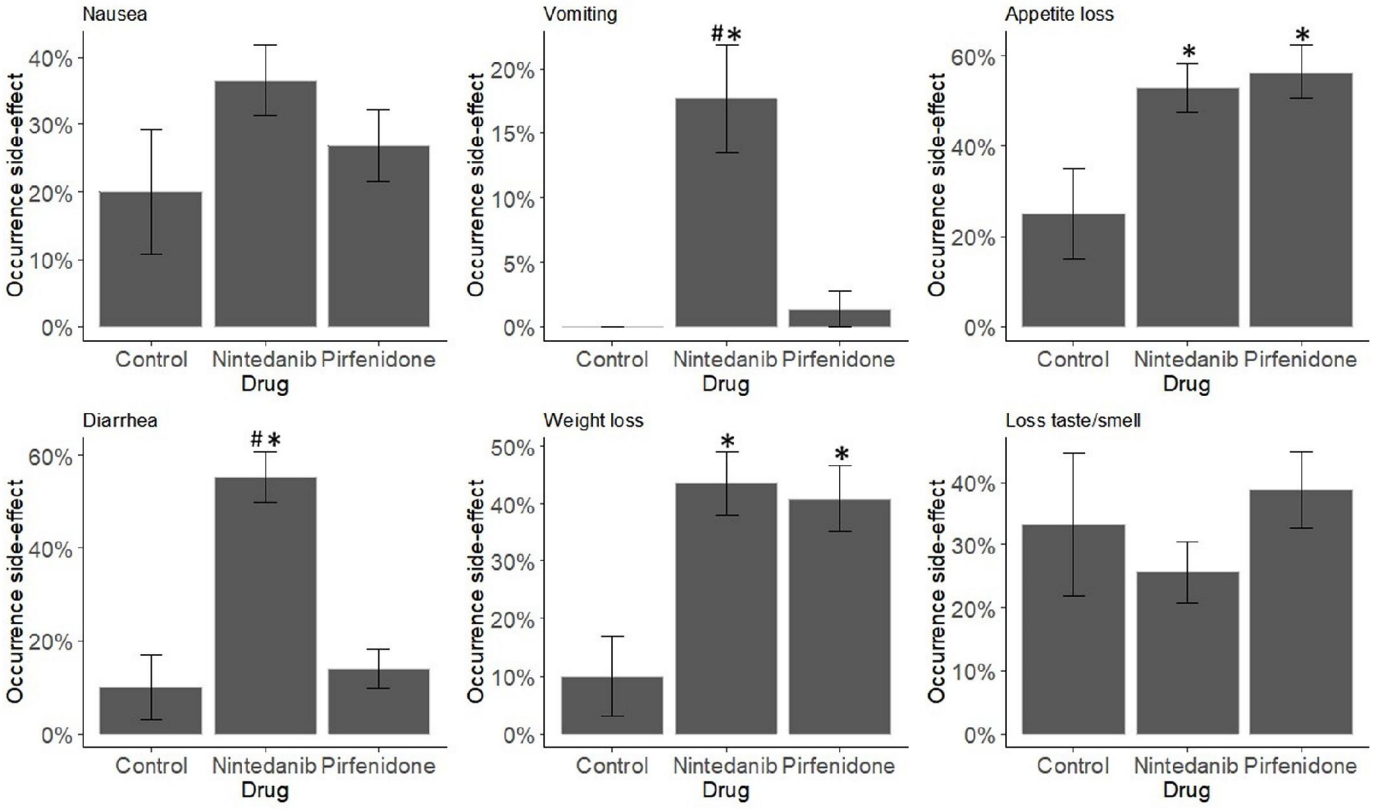

Figure 1. Complaints among IPF patients using nintedanib, pirfenidone or neither (control).

*Value differs significantly from controls (p<0.05)

#Value differs significantly from other drug group (p<0.05)

Table 2 shows the effect of both drugs on the occurrence of side effects, taking correlated covariates into account (Appendix 1).

Nintedanib (p=0.02) showed an effect on nausea, while pirfenidone (p=0.11) did not have a significant influence. Adding gender as a covariate (p<0.01) showed that the men were significantly less likely to suffer from nausea than the women.

As regards diarrhea, nintedanib was associated with significantly increased (p<0.01) diarrhea complaints, while pirfenidone (p=0.41) did not show any effect. Both nintedanib (p<0.01) and pirfenidone (p<0.01) users reported significantly reduced appetite, with women (p<0.01) reporting significantly more appetite loss than men. Antacid use (p<0.05) also increased appetite loss.

Weight loss appeared to be significantly higher among nintedanib users (p<0.01) compared with non-drug users, while pirfenidone (p=0.015) seemed to be associated with to have a less weight loss. A higher BMI was associated with a lower risk of weight loss (p<0.05), whereas vitamin D use increased weight loss. Antacid use (p<0.01) was also associated with

significantly increased weight loss.

Finally, even though 31% of the respondents reported to suffer from a decrease in appetite or smell perception, table 1 shows that this cannot be attributed to their drug use. Other covariates that tended to have an effect included gender (p=0.01), as women were significantly more likely to suffer from loss of appetite or smell, and antacid use (p=0.021), which increased the risk of loss of taste or smell perception.

Table 2 Occurrence of side effects among drug users

	Coefficient	Std. Error	Z Value	p-Value
Nausea				
Intercept	-0.62	0.61	-1.03	0.30
Nintedanib	1.51	0.68	2.24	0.02*
Pirfenidone	1.03	0.69	1.50	0.13
Gender	-1.84	0.42	-4.39	<0.01*
Diarrhea				
Intercept	-2.20	0.75	-2.95	<0.01*
Nintedanib	2.41	0.78	3.10	<0.01*
Pirfenidone	0.39	0.82	0.48	0.64
Appetite loss[a]				
Intercept	-1.48	0.71	-2.10	0.036*
Nintedanib	2.34	0.72	3.24	<0.01*
Pirfenidone	2.50	0.73	3.42	<0.01*
Gender	-1.69	0.49	-3.46	<0.01*
Antacid	0.92	0.38	2.42	0.016*
Weight loss[a]				
Intercept	-0.89	1.62	-0.55	0.58
Nintedanib	2.08	0.8	2.59	<0.01*
Pirfenidone	1.98	0.81	2.43	0.015*
BMI	-0.11	0.05	-2.09	0.036*
Vit.D	0.8	0.36	2.24	0.025*
Antacid	1.37	0.44	3.08	<0.01*
Loss of taste or smell	perception[b]			
Intercept	-2.25	0.95	-2.37	0.018*

Nintedanib	0.32	0.66	0.48	0.63
Pirfenidone	1.00	0.67	1.50	0.13
Gender	-1.26	0.44	-2.87	<0.01*
Time since diagnosis	0.46	0.26	1.75	0.080
Antacid	1.06	0.46	2.3	0.021*

[a]1 observation deleted due to missing value

[b]10 observations deleted due to missing values

*significant influence

Table 3 Patients' comments in the survey: advice for prescribers

Prescribers should give patients guidance about taking medication to reduce side effects, such as what time of the day to take medication, or if it should be taken with food, and possible interactions. Hospital and/or community pharmacists could play a role, especially with regard to patients' other possible drug use, e.g. statins.
Prescribers should reassure patients about the amount of medication that they may be on, and possible interactions with other drugs, explaining why it is necessary.
Prescribers should review any treatments prior to receiving the IPF diagnosis, such as long-term steroid use, and check for a risk of antibiotic resistance.

Discussion

Ideally, a progressive and almost invariably fatal disease like IPF should be treated, unless there is clear evidence of a lack of response. Benefits and burden of treatment should be discussed with every newly diagnosed IPF patient, taking his/her unique profile into account (Table 3). It is therefore important to gain more insights into the way the drugs work and their possible side effects. The current study found a difference in self-reported side effects between the two anti-fibrotic drugs nintedanib and pirfenidone among an IPF sample. In the majority of the cases, the use of the drug was continued despite the side effects. Nintedanib users (48.3%) reported suffering from a significant increase in diarrhea, weight loss, vomiting and loss of appetite, compared with non-drug users (11.4%). Pirfenidone users (40.3%) reported a significant increase in loss of appetite and weight loss. The degree of weight loss and loss of appetite did not differ signifcantly between the two groups of drug users. Other side effects reported by respondents in our study included dry mouth, dyspepsia, sun allergy and skin rash (data not shown), which was in line with a previous study by Bennet et al. [9].

Previous studies on the side effects of anti-fibrotic drugs have reported similar results. The nausea and vomiting associated with nintedanib (figure 1) was also found in previous research [10, 11]. By contrast, the association between pirfenidone and nausea or vomiting as found by previous studies was not confirmed by our results [12, 13]. A possible explanation could be that 68.1% of our respondents had used pirfenidone for more than 12 months, while most stomach complaints manifest within the first 3 months and decrease over time [14]. Furthermore, the problem of nausea can be reduced by taking pirfenidone immediately after food consumption [15].

The weight loss, loss of appetite and diarrhea reported for nintedanib users in previous studies was in line with our current data, which also showed a significant prevalence [10, 11, 16, 17]. In order to counter these side effects, it could useful to look into dietary interventions. For example the official nintedanib website recommends the Bananas Rice Applesauce Toast (B.R.A.T.) diet to counter diarrhea [18].

Our pirfenidone users reported an increase in loss of appetite and weight loss, which is also in agreement with results from previous studies [13, 19, 20]. Finally, 31% of all respondents reported suffering from loss of taste or smell perception. Our data showed, however, that this was not caused by anti-fibrotic drug use. The loss of taste or smell perception could be influenced by covariates related to IPF. Women appeared more prone to loss of taste or smell perception than men, and antacid use also affected taste and smell perception. Another possible cause could be that the disease itself influences taste and smell perception. Reduced taste perception is also found in other lung diseases like COPD and lung cancer [21-24]. Lung function could play an important role in taste or smell perception. A possible underlying cause could be a relation between lung retention and retronasal smell perception, as suggested in a previous study [25]. Taste and smell perception are related and therefore retronasal smell perception could also influence taste. This process has also been suggested to play an important role in the flavour perception of vaping [25]. Another study found that lung retention, measured by the release of N-isopropyl-p[^{123}I]-iodoamphetamine (^{123}I-IMP) by the lung after ^{123}I-IMP injection, was prolonged in lung fibrosis patients [26].

Besides knowing which side effects can occur due to the current treatment, it is also important to analyse whether this leads to drug discontinuation. In our study drug discontinuation was rather rare. Two pirfenidone and one nintedanib user stopped their anti-fibrotic medication completely due to the side effects (data not shown).

In the ASCEND and CAPACITY studies, the reported pirfenidone side effects of skin rash, nausea and dyspepsia did not lead to drug discontinuation in the clinical trials [12, 13, 27]. Similarly, although more than 60% of patients receiving nintedanib experienced diarrhea in the INPULSIS trials, this was often adequately controlled by dose reduction or anti-diarrheal medication, with <5% of them having to discontinue the medication completely [28].

Many European national guidelines on IPF recommend that treatment should be stopped if the disease gets worse [29]. This is generally recommended if the FVC is reduced by more than 10% in 12 months. However, the assessment of treatment response in IPF is complicated by its variable clinical course. It can therefore not be excluded that the degree of functional decline could be even higher without anti-fibrotic treatment. In fact, recent data suggest a potential benefit of continued treatment with pirfenidone in patients with IPF who experience clinically meaningful progression during treatment. In the case of "treatment failure" (e.g., FVC decline ≥10% predicted), switching to the other drug should also be considered. In the Dutch IPF sample we studied (n=176), 24 people switched from pirfenidone to nintedanib, and five respondents reported having switched from nintedanib to pirfenidone in the past. Among the 24 respondents who switched to nintedanib, three did so because the medication did not achieve the desired effect. Twenty-one mentioned side effects as an underlyingreason. Among the five respondents switching to pirfenidone, three reported having switched because the medication did not have the desired effect. Two respondents mentioned side effects as an underlying reason.

Limitations

One of the limitations of this study is that information about disease severity was lacking, so the impact of disease severity on the side effects could not be established. Another limitation is that the symptoms were self-reported and not objectified by a health care professional.

Recommendations

To add to the current knowledge on side effects of nintedanib or pirfenidone, it could be useful to investigate the effects and safety of co-administration of pirfenidone and nintedanib. In our current dataset two respondents mentioned using both drugs. This group was too small to estimate the effect of symbiotic drug use on side effects. While there are no robust data on the safety and efficacy of combining pirfenidone and nintedanib in IPF treatment, some studies suggest that co-administration is tolerable and safe [17, 30-32]. The large number of fibrotic pathways likely to be involved in the pathobiology of IPF and the potential synergistic effects of the two drugs may provide beneficial to the patients. In terms of efficacy, four scenarios are possible: 1. synergy; 2. add-on; 3. a weaker effect than expected (either because the mechanism of efficacy is targeted by both drugs and a ceiling effect is achieved, or because there is a blocking interaction); and 4. unpredictable interaction that drives disease progression or produces unacceptable side effects.

Some in vitro studies have found a beneficial effect of co-administration [33, 34]. However long-term studies in humans are limited to one case report, which mentioned a long-term positive effect [35]. In addition to pirfenidone and nintedanib, there is also a conditional recommendation for antacid use in IPF treatment [36]. In contrast to what is known about pirfenidone and nintedanib, the data supporting the effect of antacid therapy in IPF is of poor quality (e.g., observational/retrospective studies and post-hoc analysis of patients assigned to placebo arms in clinical trials of pharmaceutical interventions). The guidelines do acknowledge the need for further research on the efficacy and long-term safety of antacid

therapy as well as interactions with other IPF medications.

All authorised products of nintedanib and pirfenidone in the European Union are listed for close monitoring. These products are marked by regulatory authorities as requiring additional monitoring with regard to adverse drug reactions [37].

The data retrieved from our study show that both nintedanib and pirfenidone carry a high burden of gastrointestinal side effects. Therefore, it would be useful to look into possible dietary interventions to minimise this burden, as well as the use of other drugs to counter these side effects.

Conclusion

Information about possible side effects is important if patients are to receive the best anti-fibrotic treatment available. The current study showed that the two anti-fibrotic drugs nintedanib and pirfenidone have different side effects. Nintedanib users reported a significant increase in diarrhea, vomiting, weight loss, and loss of appetite, while pirfenidone users suffered primarily from an increase in loss of appetite. In addition, nintedanib was associated with nausea and pirfenidone with weight loss. Our data showed that 24 respondents had switched from pirfenidone to nintedanib in the past, while five had switched from nintedanib to pirfenidone, suggesting that although nintedanib gave rise to more gastrointestinal side effects, the general burden of side effects of nintedanib is probably lower. Both pirfenidone and nintedanib carry a rather high burden of gastrointestinal side effects, so it could be useful to look into dietary interventions to minimise this burden.

Acknowledgements

The authors would like to thank the Dutch Fibrosis Patient Society (www.longfibrose.nl) and all participants in this study for all their efforts to make this project a success.

Author Contributions

All authors were involved in the study design and data collection. VP, MD, and AB analyzsed the data and drafted the manuscript. ME conducted the survey. ME, NJ, and PW revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Funding

This study was supported by a research grant of the ild care foundation: www.ildcare.nl. The study sponsor had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

Data Availability

The datasets used and/or analyzsed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

In accordance with the Dutch Act on Human Subjects Medical Research, the Medical Ethics Committee of St. Antonius Hospital Nieuwegein waived formal approval.

Conflict of interest

The authors declare that they have no competing interests.

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