Can diet regimes be an option for treatment of acne vulgaris?

A systematic review of the literature

Version 1

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Abstract

Introduction: A correlation between foods and acne vulgaris has been well established with numerous epidemiological studies worldwide. Hyperinsulinemia and different hormones like IGF-1 and IGFBP-3 seem to play an important and central role in the connection between food and the pathogenesis of acne.

Objective: Can our everyday diet be used as a way to challenge the inflammatory and chronic disease acne vulgaris? What if people could keep their acne disease under control by only making dietary changes?

Method: The literature was searched using PubMed with different combinations of Mesh terms. The searched was also complemented with words without Mesh terms. 25 clinical trials met the inclusion criteria and were read in full text. After matching with the exclusion criteria, six papers were included in this review.

Result: Five out of the six articles had results that showed an alteration in acne with the diet the intervention group received but only three of them reached significance in their results. Of the ones that achieved significance, two showed that a LGL diet could decrease inflammatory acne lesion counts. The third one presented in their results that cacao might be able to aggravate or evoke acne in patients with no or mild acne disease.

Conclusion: The fact that a correlation between different kind of foods and acne vulgaris exists can no longer be dismissed. But in order to use this information in clinical praxis, more research with greater sample sizes is needed.

Key Words: Acne Vulgaris, dietary treatment, diet, food,
Abbreviations

LGL: Low Glycemic Load
HGL: High Glycemic Load
IGF-1: Insulin-like Growth Factor 1
IGFBP-3: Insulin-like Growth Factor Binding Protein 3
SHBG: Sex Hormone Binding Globulin
SCL-90: Symptom Check List 90
IGA: International Global Assessment
<table>
<thead>
<tr>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION...</td>
</tr>
<tr>
<td>PATHOGENESIS OF ACNE VULGARIS ...............................................................................................................................................</td>
</tr>
<tr>
<td>DIET AND ACNE ........................................................................................................................................................................</td>
</tr>
<tr>
<td>TODAY'S ACNE TREATMENT ..............................................................................................................................................................</td>
</tr>
<tr>
<td>ACNE GRADING ..............................................................................................................................................................................</td>
</tr>
<tr>
<td>OBJECTIVE...................................................................................................................................................................................</td>
</tr>
<tr>
<td>AIM.............................................................................................................................................................................................</td>
</tr>
<tr>
<td>METHODS .....................................................................................................................................................................................</td>
</tr>
<tr>
<td>LITERATURE SEARCH ......................................................................................................................................................................</td>
</tr>
<tr>
<td>QUALITY ASSESSMENTS ...............................................................................................................................................................</td>
</tr>
<tr>
<td>RESULT......................................................................................................................................................................................</td>
</tr>
<tr>
<td>DISCUSSION...............................................................................................................................................................................</td>
</tr>
<tr>
<td>CONCLUSIONS...............................................................................................................................................................................</td>
</tr>
<tr>
<td>ACKNOWLEDGES...........................................................................................................................................................................</td>
</tr>
<tr>
<td>REFERENCES..................................................................................................................................................................................</td>
</tr>
</tbody>
</table>
Introduction

Pathogenesis of acne vulgaris

Acne is one of our biggest national diseases and in Sweden a study has shown that every third person have enough suffering from their acne that they want to receive treatment [1]. For many years there has been a strong opinion and belief that what we eat and how our skin looks has no connection in acne. This is an opinion that has started to be challenged during the past few years.

Acne Vulgaris is a disorder primarily among teenagers and young adults. However 10-20% continue to experience the disorder in their adult life [2] and the prevalence of adults with acne is increasing [3]. It’s the most common skin disorder and has the highest cumulative incidence in a general population [3]. The cause of acne among teenagers is an increased sebum production by the sebaceous glands after puberty [2]. Comedones (small cysts) take form in hair follicles because of a blockage of their opening by sebum and keratin. Within these comedones an activity of Propionibacterium acnes cause a release of free fatty acids from sebum which gives rise to an inflammation within the cysts. This eventuates in a wall rupture and extrusion of cyst debris, which results in an inflammatory foreign-body reaction.

Both endogenous and exogenous factors can influence the expression of acne. Some topical agents (cosmetic and hair products), trauma/friction, chronic topical exposure to some industrial products such as oils or chlorinated substances, and the use of glucocorticoids can all evoke or exacerbate preexisting acne. Certain systemic pharmaceuticals such as oral contraceptive pills, phenytoin, isoniazid, lithium, androgen steroids and phenobarbital may sometimes give acneiform rashes or aggravate preexisting acne. PCO (polycystic ovary disease) and genetic factors can also play a role in the pathogenesis. [2]

Since the disease acne vulgaris is not a life-threatening disease many people only sees it as a localized disease of the skin. An underestimated problem with acne patients is the great negative psychological impact it can have in their lives. A study made in 2013 with 103 participants and 106 controls [4] showed that acne vulgaris has a great negative influence regarding the acne patients psychological status. The most common symptoms were psychoticism (34,0%) and depression (31,1%) but other psychological symptoms observed were obsession, anxiety, sensitivity, phobia, paranoid ideation, somatization and hostility. Also, a significant positive correlation between duration of illness and higher SCL-90 scoring were observed. SCL-90 is a self-report scale with 90 questions that evaluates physiological
and psychological health. Every question is rated in a five-point scale of distress that’s ranging from 0 (“not at all distressed”) to 4 (“extremely distressed”) [4].

**Diet and Acne**

In an article [5] from the Journal of the American Academy of Dermatology in 2010, Bowe and co-workers stated that “Dermatologists can no longer dismiss the association between diet and acne”. Many epidemiologic studies have shown possible associations between different foods and acne. In 2002 a comparative study between western modern societies and non-westernized societies identified that a diet with LGL correlated with the absence of acne in 2 non-westernized populations [6]. Two big cohort studies in USA 2005 and 2006 showed an increase in female acne with high dairy consumption (milk) [7, 8]. Another cohort study in USA 2008 showed an association between high milk consumption and acne in teenage boys as well [9]. A pilot study in 2008 concluded that a high glycemic load diet is associated with reduced levels of serum hormone-binding globulin and an increase in IGF. In 2009 a cohort study in Norway with 3775 participants identified a high consumption of chocolate, potato chips and sweets in patients with acne [10]. A strong correlation between consumptions of sweets and acne prevalence was also shown in a cohort study in 2009 [11]. Another cohort study from 2010 showed that junk food, carbonated drinks and some other foods can aggravate acne. [12]

In a recent cohort study from New York based upon questionaries’ of the subjects’ dietary habits it is suggested that a diet with HGL and high milk consumption may aggravate acne [13]. The participants with moderate or severe acne reported a greater HGL intake in their diet, more added sugar, more servings of milk per day and a lower intake of fish.

The theory for the connection between a HGL diet and acne vulgaris is that it promotes a postprandial hyperinsulinemi [14, 15]. The high levels of insulin in blood initiate a hormonal cascade, which in the end leads to an elevation of IGF-1 and simultaneously reduces the levels of IGFBP-3 [16]. IGFBP-3 normally inhibits tissue growth and IGF-1 is needed for keratinocyte proliferation [17]. The belief is that an elevation in the levels of free IGF-1, induced by insulin, can promote acne through hyperkeratinization [18]. A high consumption of cow milk also will also elevate the amount of IGF-1 in blood. Even after pasteurization cow milk contains high levels of IGF-1 and it is believed that it survives the human digestion. [19]
IGFBP-3 normally prevents IGF-1 from binding to its receptor and acts like a growth inhibitory factor. A reduction of IGFBP-3 induced by the hyperinsulinemia may contribute to the unregulated cell growth in sebum follicles in acne. A reduction of IGFBP-3 may also affect the nuclear retinoid signal pathway and thereby promote the follicular growth. Normally retinoids inhibits cell proliferation and promote apoptosis. IGFBP-3 acts as a ligand for nuclear retinoid receptors and promotes an activation of gene transcription. Its function is to limit the cell growth in many cell types. The normal limitation of cellular proliferation in sebum follicles may be reduced when plasma levels of IGFBP-3 is low. [20]

Androgens as well as the androgenic effect from hyperinsulinemia are well known to stimulate the sebum production. Insulin and IGF-1 stimulate the synthesis of androgens and at the same time it inhibits the production of SHBG. A higher level of androgens, insulin and IGF-1 has been shown to be associated with acne [21].

**Today's Acne treatment**

The goal of today's treatment against Acne Vulgaris is to eliminate comedones by normalizing the follicular keratinization, reduce sebum production, decrease the number of P. acnes and decrease the inflammation. A mild disease might respond to a local therapy alone. You can use a topical agent that may alter the epidermal desquamation and then prevent the formation of comedones and help the breakdown of preexisting cysts. You can also use a topical agent whose power is antibacterial. [2]

With moderate or severe acne with a great inflammatory component a systemic therapy is often needed. In that case the treatment of choice is most often antibiotics which profit is mainly anti-inflammatory affect rather than antibacterial. Some female patients may also benefit from hormonal therapy such as oral contraceptives. Some patients with severe nodulocystic acne do not respond well to the therapies above and then treatment of choice is isotretionin. Isotretionin is a synthetic retinoid and even though their exact mechanism is not known, the belief is that it acts by inhibiting the sebaceous gland size and function [22]. This has great effect in some patients. Its use is highly regulated though because of a great potential for severe side effects [2].

One of the major problems with today's treatment is that far from everyone benefits from it. Some teenagers repeatedly go through courses of antibiotics but don’t get any noticeable effect. There are also people who can keep their disease under control during medical therapy but as soon as the stop taking the medicine, the disease gets back. This creates a group of
people who becomes chronic antibiotic users and in times of antibiotic resistance this might not be so good. Recent recommendations in Sweden [23] push for a narrower and more time limited use of antibiotics for acne patients. Another article from the “Skin Therapy Letter” [24] writes that “a change is needed in old prescribing habits and that each acne patient should be carefully considered before prescribing antibiotics”. The current prescription to youths is very generous and is a big threat for the rising antibiotic resistance [23].

Acne grading

There exist many different techniques for how to grade acne severity but unfortunately no clear consensus in which one to use and when to use it. One that is quite common is the Leeds grading technique from 1984 [25] and also the revised Leeds grading technique from 1998 [26]. These are pretty much compendiums with photographs of different acne patients with acne vulgaris. These photographs are graded and ranked according to the severity of their disease. The grading of severity is based upon the degree of inflammation, size and range of inflamed lesions and if there is an associated erythema. This withholds 12 different stages of facial acne, 8 for the chest and 8 for the back.

Objective

That a correlation between food and acne can exist has been well established with many different epidemiological studies around the world. But what does it tell us? Can we use our dietary habits to tackle this widespread disease? This paper is written to review the literature today and try to evaluate if dietary changes are something we can replace or add to today’s treatment of acne vulgaris. What if many people could keep their disease under control through their diet alone? This area has been very quiet for many years but over the past ten years many studies have been made and researchers are getting a greater interest concerning this. But how many intervention studies have actually been made?

Aim

The issue I will answer with this essay is:

- Can acne vulgaris be treated by making dietary changes?
Methods

Literature Search

This paper is written as a systemic review and the database that has been searched is PubMed. Different combinations of Mesh terms were used to investigate the area of articles. PubMed was also searched without any Mesh terms to be sure that all studies in this area were included. Two inclusion criteria were also taken into count during the search:

- The publication had to be a clinical trial
- It also had to be written in the English language.

<table>
<thead>
<tr>
<th>Database</th>
<th>Search words/Mesh</th>
<th>Hits</th>
<th>Clinical trials</th>
<th>Included after reading in full-text (excluded duplicates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>(&quot;Acne Vulgaris&quot;[Mesh]) AND &quot;Diet&quot;[Mesh]</td>
<td>106</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>PubMed</td>
<td>(&quot;Acne Vulgaris&quot;[Mesh]) AND &quot;Food&quot;[Mesh]</td>
<td>130</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>PubMed</td>
<td>(&quot;Acne Vulgaris&quot;[Mesh]) AND &quot;Glycemic index&quot;[Mesh]</td>
<td>21</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>PubMed</td>
<td>(&quot;Acne Vulgaris&quot;[Mesh]) AND &quot;Diet therapy&quot;[Mesh]</td>
<td>40</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>PubMed</td>
<td>Acne Vulgaris and Diet</td>
<td>220</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>PubMed</td>
<td>Acne Vulgaris and Food</td>
<td>276</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>PubMed</td>
<td>Acne Vulgaris and Glycemic Index</td>
<td>30</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>PubMed</td>
<td>Acne Vulgaris and Dietary carbohydrates</td>
<td>29</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>PubMed</td>
<td>Acne Vulgaris and Dietary proteins</td>
<td>18</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>PubMed</td>
<td>Acne vulgaris and Dietary fats</td>
<td>22</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PubMed</td>
<td>Acne Vulgaris and Chocolate</td>
<td>25</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>PubMed</td>
<td>Acne Vulgaris and Milk</td>
<td>46</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

In total this accounted for 27 articles that met the inclusion criteria and all of them were written in English. 20 of these publications were excluded when read in full-text at the base of one of the following four exclusion criteria:
• If the trial besides diet also used acne treatment in the form of drugs (antibiotics, isotretionin, etc.) they were excluded.
• The study was excluded if it looked into the effect of a dietary supplement like vitamins or probiotics.
• If they question formulation in the trial did not match the aim of this study or weren’t clear enough they were also excluded.
• The trials that weren’t intervention trials were excluded.

When studies that met these criteria had been excluded, the numbers of article remaining were seven. There was also one article that was a duplicate because it had been published in two different magazines. When one of them was removed the number of articles remaining were six.

Quality Assessments

The analysis and determination of the quality of the studies was based on a questionnaire from SBU [27]. The aim with this was to evaluate possible biases in the chosen studies. The following pieces were categorized into low, average high or high risk for bias:

• A1 = Selection bias
• A2 = Performance bias
• A3 = Detection bias
• A4 = Attrition
• A5 = Reporting bias
• A6 = Other considerations

When A1-A6 had been evaluated a summarized judgment of the risk for bias was made into one of the following: Low risk, average risk or high risk.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study type, Study time</th>
<th>Study population</th>
<th>Intervention/exposure S = Subjects, C = controls</th>
<th>Outcome measures</th>
</tr>
</thead>
</table>
| Fulton, J. E. | [28] | Crossover, single-blinded. 4 weeks with one bar, 3 weeks rest, 4 weeks with the other bar. | 65 subjects of both sexes (30 adolescents with mild-moderate acne and 35 young male controls) | S: Enriched chocolate bar  
C: Placebo bar, no chocolate | Acne lesions, sebum production and sebum composition. |
| Smith, R. N. | [29] | Parallel randomized controlled dietary intervention trial with investigator-blinded dermatological assessment 12 weeks | 43 male subjects (23 with mild-moderate acne and 20 controls in the age of 15-25 years). | S: LGL diet (25% energy from protein, 45% from LGL carbohydrates, 30% from fats)  
C: Urged to include carbohydrates as a regular part of their diet. | Changes in lesion counts using Leeds grading technique. |
| Smith, R. N. | [30] | Parallel randomized controlled dietary intervention trial with investigator-blinded dermatological assessment 12 weeks | 31 male subjects (16 with mild-moderate acne and 15 controls) aged 15-25 years | S: LGL diet (25% energy from protein, 45% from low GI carbohydrates and 30% from fats)  
C: Urged to include carbohydrates as a regular part of their diet | Changes in lesion counts using Leeds grading technique. |
| Reynolds, R. C. | [31] | Parallel controlled dietary intervention trial with investigator-blinded dermatological assessment 10 weeks | 43 lase subjects (23 with acne grade 1, 2 or 3 and 20 controls). Adolescents. | S: LGL diet  
C: HGL diet | Degree of inflammation in inflammatory lesions and acne was grading from 0 to 3 (0 = no acne, 1 = mild, 2 = moderate and 3 = severe) |
| Kwon, H.H. | [32] | Parallel randomized controlled dietary intervention trial with investigator-blinded dermatological assessment. | 32 subjects (17 with mild-moderate acne and 15 controls)  
Age range between 20-27 years | S: LGL diet (25% energy from protein, 45% from low GI carbohydrates and 30% from fats)  
C: Maintain a regular diet. | Changes in lesions counts and histopathological changes in acne lesions using Leeds revised acne grading system |
<table>
<thead>
<tr>
<th>Author</th>
<th>Result</th>
<th>Quality of the study (Low, average or high risk for bias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulton, J. E. [28]</td>
<td>Insignificant differences between the groups. Twice as many got better with the chocolate bar.</td>
<td>A1 = High, A2 = Low A3 = Average, A4 = Average A5 = Low, A6 = Low Total: Average risk for bias</td>
</tr>
<tr>
<td>Smith, R. N. [29]</td>
<td>The reduction in total lesion counts was significantly greater in the LGL group compared with the control group ((p = 0.01)) and similar results for the mean decrease in inflammatory counts ((p = 0.02)).</td>
<td>A1 = Low, A2 = Low A3 = Low, A4 = Average A5 = Low, A6 = Low Total: Low risk for bias</td>
</tr>
<tr>
<td>Smith, R. N. [30]</td>
<td>At 12 weeks, total acne lesion counts decreased by 59% in the LGL group and by 38% in the control group ((p = 0.046)). There were no significant differences between the groups regarding inflammatory lesions.</td>
<td>A1 = Low, A2 = Low A3 = Low, A4 = Average A5 = Low, A6 = Low Total: Low risk for bias</td>
</tr>
<tr>
<td>Reynolds, R. C. [31]</td>
<td>Facial acne improved on both diets but differences between them did not reach significance. Low GI: (\sim 26% \ (p = 0.0004)) and high GI: (\sim 16% \ (p = 0.01)).</td>
<td>A1 = Average, A2 = Average A3 = Low, A4 = Average A5 = Low, A6 = Low Total: Average risk for bias</td>
</tr>
<tr>
<td>Kwon, H.H. [32]</td>
<td>The LGL diet group demonstrated a significant decrease in acne grades, from 2.18 to 1.60 ((p = 0.02)) with a decrease in the mean numbers of lesions to 70.9% of baseline. The difference in severity between the 2 groups was also significant ((p = 0.02)). No significant reduction in control group. A significant decrease in the overall size of the sebaceous glands was also observed ((p = 0.03)).</td>
<td>A1 = Low, A2 = Low A3 = Low, A4 = Low A5 = Low, A6 = Low Total: Low risk for bias</td>
</tr>
<tr>
<td>Caperton C [33]</td>
<td>A significant increase in the mean number of total acneiform lesions was detected on both Day 4 ((p = 0.006)) and Day 7 ((p = 0.043)) compared to baseline. No significance was achieved when mean number of acneiform lesions on days 4 and 7 were compared to each other ((p = 0.138)).</td>
<td>A1 = Low, A2 = Low A3 = Low, A4 = Average A5 = Low, A6 = Low Total: Low risk for bias</td>
</tr>
</tbody>
</table>
Four of the six studies investigated whether a LGL diet could improve symptoms of acne vulgaris or not. All four of them showed an improvement in acne but only two achieved significance in the decrease of acne lesions [29, 32].

The other two trials tried the hypothesis whether chocolate was something that could worsen or spark acne vulgaris. The result from the first one in 1969 showed no correlation but instead some of the subjects improved their acne with the chocolate bar which was the opposite of the hypothesis [28]. Interestingly though, the second study from 2014 instead showed an significant increase in acne lesions with the intake of cacao filled capsules [33].

Four studies showed a low risk for bias after the quality assessment. The one with the highest risk were the one from 1969 and the reason for this judgment were that:

- It was a single-blinded study; the dermatologists knew if the participant had received a chocolate or placebo bar.
- How the randomization had been carried out was not described in the method.
- The ages of the participants were not revealed.
- The reader could not assess the method used for grading acne.
- Even though the number of dropouts from the study was low, the reasons for the dropouts were not described.

The other study that received an average risk were the one made by Reynolds [31] in 2010. All the participants, even the ones that were assigned the HGL diet got the information that a LGL diet might improve acne. The paper did not tell how the randomization of the groups had been carried out. The third reason for the average risk was that the trial had 26% dropouts.

The study from 2007 [29] had 22% dropouts but no other points for risks, which resulted in the total score of a low risk. The same applied for the study from 2008 [30], which had 43% dropouts. There were no dropouts in the study made by Kwon [32] and this followed by a low score in all parts of the quality assessment. The latest study from 2013 [33] had one participant (8%) who dropped out. Still it received an average risk in that section because the reason for the dropout was not revealed.
Discussion

Can acne vulgaris be treated by making dietary changes? Can this question now be answered? If only looking into the results of the three studies (out of six) that achieved significance in their result, the answer would probably be yes. The answer is not that simple though because these six studies have showed some variations in their results. Several observational studies have been made during the past 50 years and many of them with very convincing support to this hypothesis. But studies with an actual clinical intervention are only these six. Also there are other parts of our diet than HGL diet or chocolate that is strongly believed and proved to aggravate acne. There are for example very persuasive data that dairy products made of cow milk are a great reason for teenage acne [8, 9] but no clinical trials regarding this have ever been made.

One issue with these six studies is that they all have a quite small study population. It’s ranging from 13 to 65 participants. To receive more power in the results, trials with a much bigger study sample should be made. One other issue is the acne grading system. Four of the studies used “Leeds acne grading system”, and one used the IGA. The sixth one did not use any specific method; it only counted all the lesions (inflammatory, non-inflammatory, pustules and comedones) at the left side of the face. The problem with using different methods is that the result of the study can vary depending on which method that is chosen. Would these studies have shown the same results if they all used the same grading system?

There is one thing that these six studies all have in common – their aim was to prove whether acne vulgaris could improve or worsen by making dietary changes. Four of them showed a decrease in lesion counts with an LGL diet but only two of them with significance. Fulton’s trial from 1969 was the first clinical trial regarding our dietary habits and acne [28]. This study has been widely criticized since then [28, 34]. The second and newer study that tested the hypothesis of chocolate as a cause of acne presented the opposite [33]. This one states that cacao might aggravate acne and an increase in acne lesions.

Why is changing the diet an interesting alternative to the regular acne treatment? The standard medical treatment for patients with acne vulgaris today is as previously noted long-term use of low-dose antibiotics. With the uprising widespread resistance problem other alternatives must emerge and dietary changes might be a complementary or an alternative to the already existing treatment. What if a facial cleanser and a diet change could be enough to treat at least some of the acne patients’ today?
This is an area in medicine that needs to be more explored. Most of all, more studies with bigger sample sizes need to be done. Even though there exist very convincing evidence that there is a strong correlation between different foods and acne vulgaris there aren’t enough intervention trials to evaluate whether this has an actual clinical relevance. Also the area has to be widened and maybe trials with a restriction of cow milk are the next step. Maybe a combination of a LGL diet and a restriction of cow milk should be applied as the intervention in a study.

Within this area of dermatology it is probably hard to find funding for this kind of research. It is hard to imagine that pharmaceutical companies would have any interest in this because if the fact that a diet could treat acne vulgaris would be proven to be true, they would not sell their drugs. Is this the ultimate reason that so few intervention studies have been made regarding this?

Conclusions

The question about diet as a treatment in acne cannot be answered with this few studies; more research needs to be done. That there exists a strong correlation between what we humans put in our mouths and how our skin looks is something that cannot be rejected. But in order to use this as an alternative to the regular treatment it has to be backed up with more research. As the department of dermatology in New York wrote [5]: “Dermatologists can no longer dismiss the association between diet and acne”. That is absolutely true.

Acknowledges

I would like to give my special thanks to my supervisor Magnus Lindberg who have supported me all the way and made this paper possible. A proofreading at Friday around midnight is not something a student expect from his or hers supervisor but still you did. You have helped me shape my formulations but at the same time you have given me space to write and do in my way. Thank you.