Hereditary hemochromatosis and iron-induced diabetes: a missed diagnosis?

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1. Motivation

Beste lezer,

Ik ben Sarah De Bolle en ben afgestudeerd als arts, richting huisartsgeneeskunde in juni 2008. Ik heb mijn opleiding tot huisarts onderbroken en ben Tropische Geneeskunde gaan studeren aan het Tropisch Instituut te Antwerpen. Nadien ben ik twee jaar gaan werken in een eerstelijnsziekenhuis in Zuid-Afrika. Canzibe Hospital is gelegen op één uur rijden van Mtata tussen East Londen en Durban, het voormalige Transkei tijdens de apartheid. Het is een gebied dat nog steeds achtergesteld is op de rest van Zuid-Afrika en dat merk je zeker in de geneeskunde.
Ik kwam net van de schoolbanken en was in het zevende jaar geneeskunde klaargestoomd om als HAIO te beginnen. Daar stond ik dan in Zuid-Afrika met enkel zes maanden theoretische tropenkennis als extra bagage en geen werkervaring. Een ontnuchterende periode…
Uiteraard kwamen in het eerstelijnsziekenhuis heel wat huisartsentopics aan bod: hypertensie, kinderziekten, orthopedische problemen, kleine heelkunde, COPD, astma,diabetes,... Dit was echt wel mijn ding. Vol goede moed begon ik bijvoorbeeld mijn uitleg over diabetes tegen de patiënten, hoe belangrijke het was om enkele kilo's te vermageren, het dieet dat ze moesten volgen, de controles, de medicatie, de insuline, het risico op hypoglycemie, de noodzaak om regelmatig te eten,… ik wist perfect hoe alles moest zijn en wat de richtlijnen waren. Tot een patiënt me doodleuk antwoordde dat hij enkel at wat er op zijn bord kwam. Sommige dagen was dat zelfs helemaal niets, omdat hun maandloon al op was. Dus van 'gezonde en evenwichtige' voeding was er al helemaal geen sprake. Hoe regel je de glycemie bij een diabetespatient type 1 op insuline die zich geen glucometer en al helemaal geen glucosestrips kan permitteren? Hoe motiveer je een oma om gezonder te eten en wat meer te bewegen als haar dochter net overleden is aan AIDS en ze alleen voor de opvoeding van haar 5 kleinkinderen komt te staan? Vooral de behandeling van reeds bestaande problemen stond in Zuid-Afrika op de voorgrond, preventie stond en staat nog steeds in de kinderschoenen.
Het heeft me doen stilstaan bij de wereld waarin wij als Belg mogen leven, hoe goed we het wel niet hebben en welke luxe-gezondheidszorg we ter beschikking hebben. Nu ik hier terug in België werk, vraag ik me wel eens af waarmee ik bezig ben. Leggen we de lat niet te hoog en zijn we soms niet te streng? Aan de andere kant ben ik ook opgelucht dat ik nu kan werken in een omgeving waar praktische beslommeringen niet in de weg staan om goede geneeskunde te beoefenen. Ik ben zelfs blij dat ik hier mijn lat zo hoog kan en mag leggen.
Voor mijn opleiding tot huisarts wordt er van mij verwacht dat ik een manama schrijf. Maar welk onderwerp zou ik nu kiezen… Velen raadden me aan om iets te doen in het kader van HIV/AIDS of toch iets tropisch. Dan kon ik mijn Zuid-Afrika ervaring zeker gebruiken. Maar na twee jaar werken in Zuid-Afrika was alle ellende wel even genoeg geweest en wou ik toch liever een "Belgischer" onderwerp. Ik ben op zoek gegaan naar een onderwerp waar nog niet veel over geweten was binnen de huisartsgeneeskunde. Iets waarmee ik iets totaal nieuws kon bijbrengen aan de huisartsgeneeskunde.
In onze praktijk zag ik onze verpleegster regelmatig aderlatingen doen bij patiënten. Ik was wel nieuwsgierig naar hemochromatose omdat ik er nog nooit mee in contact was gekomen. Toen ik het onderwerp hemochromatose aanhaalde bij mijn collega's zei de ene: " tja, dat komt echt niet veel voor, misschien hebben we één of twee patiënten hier in onze praktijk. Ik denk niet dat dit een interessant onderwerp is voor je manama." De andere collega zei: " ja, we hebben heel wat patiënten in onze praktijk, ik denk toch wel een stuk of acht. Ik heb tijdens mijn opleiding een bijscholing gevolgd over hemochromatose en sindsdien ben ik systematisch meer ijzerparameters

gaan bepalen. Ik heb de laatste vijf jaar toch een vier-tal nieuwe diagnoses van hemochromatose kunnen stellen." Deze twee opmerkingen maakten het des te interessanter voor mij. Het bewees dat er voor hemochromatose binnen de huisartsgeneeskunde nog heel wat werk is aan de winkel. Een uitdaging dus… en die ben ik aangegaan.

Sarah De Bolle
Lommel, 1 november 2012

2. Literature

a) Introduction

Hereditary hemochromatosis (HH) is a genetic disorder that can lead to unregulated absorption of iron from the gut with resultant iron overload. Iron will accumulate slowly in the body, with no symptoms in the beginning. Eventually the excess of iron will deposit in the liver, the pancreas, the heart, the pituitary gland, the skin and joints, which can cause fibrosis, cirrhosis, hepatocellular carcinoma, diabetes mellitus, cardiomyopathy, hypogonadism, hypothyroidism and even arthropathy. (1)

In the majority of cases, HH is caused by mutations of the HFE gene, located on chromosome 6. In 1996, two major mutations were identified: a change of the cysteine amino acid at position 282 to tyrosine (C282Y) and a change of histidine at position 63 to aspartate (H63D).
Hepcidin, a hormone produced by the liver, plays a crucial role in the iron metabolism. The synthesis of hepcidin is regulated by different factors among which the HFE-protein. Hepcidin concentrations are inversely proportional with the absorption of iron from the gut. In states of iron sufficiency, hepcidin binds to the iron-exporter ferroportin, which is localised at the basolateral side of the enterocyt. Iron goes through the ferroportin from the cytoplasma of the enterocyt to the plasma (blood). When hepcidin binds to ferroportin, however, this causes internalisation of ferroportin into the cell and degradation. The iron concentration in the cytoplasma of the cell will rise, which will decrease the absorption from the gut.
In hemochromatotic patients the HFE-protein is abnormal, which will affect the production of hepcidin. The hepcidin concentration stays low in these patients, so an abnormal amount of iron is absorbed from the gut. (1, 2) Besides the two major disease-causing mutations, there are several others of which the clincial relevance is unclear.

In Northern Europe about five in every 1000 people are homozygous for the C282Y mutation. (3) The prevalence of the mutations is frequent, but the clinical penetrance is low. According to Whitlock EP et al 38-50% of individuals homozygous for C282Y mutation, may develop iron overload, with 10-33% developing hemochromatosis-related disease. (4) But estimates of the penetrance of the disease vary widely and may be modulated by environmental or dietary factors. (1)

The classical triad of clinical iron overload, includes hepatomegaly, diabetes mellitus and hyperpigmented skin. This so-called ‘bronze diabetes’ was noted by Hanot and Schachmann in 1886. Usually the first symptoms present themselves around the age of 40-50 years. A lot of patients will stay asymptomatic. Others will complain about fatigue, arthralgia, abdominal pain, loss of libido, liver disease and skin pigmentation.

A diagnosis of HH should be considered in patients with an elevated transferrin saturation (>45%) and/or an elevated serum ferritin level (female>300µg/L, male >400µg/L). Genetic testing can confirm the diagnosis. When diagnosed in time, the complications can be easily prevented by simple phlebotomy. One unit of blood (=250mg iron) is removed every week until the serum ferritin level is <50µg/L. From then on, maintenance phlebotomy can be performed as needed. The prognosis is determined by the presence of cirrhosis or diabetes.

The pathophysiology of diabetes mellitus (DM) associated with HH remains uncertain. Two mechanisms contribute to the development of hyperglycemia and diabetes in HH: liver iron overload and pancreatic beta-cell iron accumulation. (5)
The loss of insulin secretory capacity is the primary event leading to haemochromatosis related diabetes. (6) Iron accumulates in the beta-cell islet of the pancreas. Liver dysfunction due to iron damage to the hepatocytes will lead to insulin resistance.

DM as a complication is seen in 20-50% of all untreated HH patients. (1) So with early detection and screening we can prevent several new cases of diabetes. Our research question was if phlebotomy could ameliorate the glucose metabolism in patients with HH induced diabetes?

b) Methods

In our literature search we used the following PICO (Patient, Intervention, Comparison, Outcome):

- P: Man/woman, 45-70 years old, iron induced DM
- I: venesection/phlebotomy
- C: glucose metabolism (ranging from IGT (impaired glucose tolerance) to diabetes mellitus) before and after venesection.
- O: Is there improvement of the glucose metabolism after phlebotomy?

A search was conducted in the database MEDLINE with the search filter OVID from 18/05/2012 till 18/06/2012. As search terms, 'hemochromatosis', 'phlebotomy', 'bloodletting', 'iron overload', 'diabetes mellitus', 'hyperglycemia', 'hyperinsulinism' were used. The search strategy is illustrated in Table one.

1.	Hemochromatosis
2.	Plebotomy / OR Bloodletting/
3.	1.OR 2.
4.	Iron overload/ OR Hemochromatosis/
5.	Diabetes mellitus/ OR Hyperglycemia/ or hyperinsulinism/
6.	4. AND 5.
7.	6. AND 3.

Table 1: search strategy in OVID/MEDLINE.

The search was rewarded with a total of 207 articles. 21 articles were excluded because of their language. All articles in Japanese, Russian, Serbian, Hungarian, Italian, Swedish, Polish, Danish and Spanish were excluded. Only articles in English, Dutch, German and French were selected. 22 case reports were excluded. Six studies were excluded because of their irrelevancy. 83 studies were excluded because there was no abstract available. In 75 studies the abstract was read. 20 studies were excluded because the abstract was irrelevant for the search. Of 55 studies the full text was searched. In six studies there was no full text available. 49 studies were retrieved and the full text was read. 37 studies were excluded based on the content of the full text. From these 12 articles the references were checked. Finally seven of the 12 articles were retrieved. Another nine related articles were selected and added to the retrieved articles. The search delivered 16 articles. (Figure A)

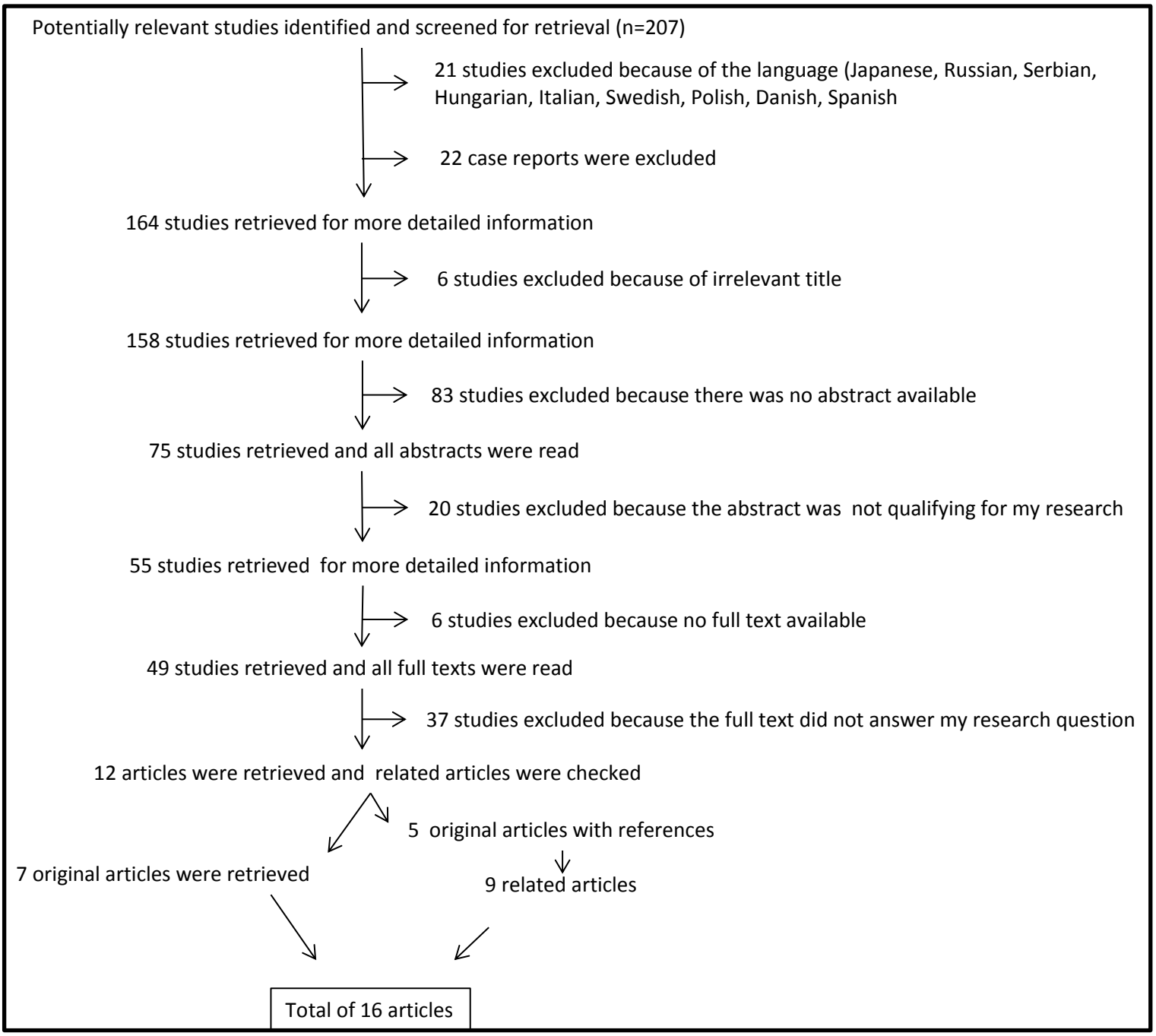

Figure A: Selection of studies

c) <u>Results</u>

Figure A shows a flow diagram of the selection of studies as described above. Ultimately 12 articles of our literature search were retrieved. Considering the aim of the study, some of the articles referred only to other articles. These articles were of course selected instead of the original article found in the search. So a total of 16 articles (seven original, nine related) were selected. Table two gives an overview of the details of the selected studies.
In 1996 the genetic background of HH was discovered. Eight studies were published before and eight studies were published after the discovery of the genetic background.

Article	**Publication year**	**Aim of the study**	**Study population**	**Effect of phlebotomy**	**Means of evaluation of glucose metabolism**
7	1969	Case-control study: Effect of phlebotomy in HH.	N=26 with DM	30,8% improved, 61,5% no change 3,9% further deterioration	Insulin requirements
8	1972	Cohort study of 115 HH patients.	N= 49 with DM	40,8% improved 42,9% no change 16,3% further deterioration	Insulin requirements
9	1980	Cohort study of 35 HH patients.	N= 7 with DM	71,4% improved 28,6% no change	Fasting glucose
10	1984	Case-control study of 10 HH men and matched controls.	N=10 without diabetes	HH show significant higher levels of insulin, fasting glucose was the same.	100g oral glucose test with measuring of glucose, insulin, C-peptide, glucagon and gastric inhibitory polypeptide.
11	1985	Cohort study: Survival and causes of death in 163 HH.	-N=? with DM -N=? with IGT or non insulin dependent DM	-45% improved (DM) -50% improved (IGT)	Insulin requirements
12	1988	Review article about hypogonadism and diabetes in HH. They follow the findings of article 10.	N=? HH patients without diabetes	100% improved so after phlebotomy, there was a normal insulin clearance (unpublished!)	Insulin clearance after 100g oral glucose load.
13	1996	Cohort study of 251 HH patients to evaluate the long-term survival.	-N=81 with DM -N=? with IGT or non insulin dependent DM	-41% improved (DM) -37-40% improved (IGT)	Insulin requirements

14	1996	Review	N=? with DM	No improvement	?
15	1997	Prospective case-control study	N=17 -HH and cirrhosis: 4 -HH and DM: 6 -HH and IGT: 7	-No improvement -No improvement -Improvement	Intravenous glucose tolerance test; acute insulin response to glucose; insulin sensitivity
16	1997	Retrospective study of diabetic HH patients	N= 49 with DM or IGT	No improvement	Insulin requirements
17	2002	RCT to evaluate the effect of phlebotomy.	N=13 with DM and high-ferritin levels ! no HH patients!	Improvement	Lab tests: HbA1c, insulin secretion, insulin resistance
18	2005	Cohort study of diabetic HH patients. Is classified as a case report.	N=10 with DM	-No improvement in 30% (on insulin) -No need for insulin in 30% during follow-up -Slow deterioration in 40%	Insulin requirements, C-peptide, HbA1c
19	2006	Interventional cohort study to evaluate the effect of phlebotomy on insulin secretion and insulin sensitivity.	N= 5 non-diabetic HH patients	Increased insulin secretion; decreased insulin sensitivity	OGTT
20	2008	Cohort study to describe the prevalence and clinical features of diabetes in HH.	N= 64 with IGT or DM	No effect	Insulin requirements

21	2008	Interventional cohort study to clarify the pathogenesis of diabetes in HH.	N= 9 with NGT N=8 with DM	Improvement	Insulin sensitivity, insulin secretion, Liver iron content, nonalcoholic fatty liver disease activity score.
22	2010	Prospective cohort study	-N= 7 IGT -N= 4 DM	-57,14% improvement -No improvement	Oral glucose tolerance test and lab tests.

Table 2: Details of the selected articles.

The sample size of the studies is quite small ranging from five to 81 patients. In a few studies it is unclear what the exact sample size is. The diagnosis of diabetes mellitus type two is not always easy. It can range from impaired glucose tolerance (IGT) to insulin dependent diabetes. (Table 2)
Some studies are making a difference between IGT and diabetes as study population. (11, 13, 15, 22)
Niederau et al (10) studied ten men with HH, but no DM. The insulin levels and fasting glucose were evaluated. In the article of Abraham et al (19) five men with HH but no DM were studied. After phlebotomy the insulin secretory capacity and insulin sensitivity was evaluated. Fernandez-Real et al (17) studied diabetic patients with high-ferritin levels, but no HH. In all the other articles patients with HH and DM were studied.
The evaluation of the glucose metabolism is done in different ways. In seven articles the insulin requirements were used to evaluate the glucose metabolism (7, 8, 11, 13, 16, 18, 20). In one of these seven (18) lab-tests for C-peptide and HbA1c were done as well. In one article (9) the fasting glucose was used. In four articles an OGTT (oral glucose tolerance test) was used (10, 12, 19, 22). Additional lab tests were also done by Niederau et al (10). An IV-GTT (intra-venous glucose tolerance test) was used in the article of Hramiak et al (15). Lab tests only were used in two articles (17, 21). In one article it is unclear how they evaluate the glucose metabolism. (14)
The aim was to evaluate the effect of phlebotomy on the glucose metabolism in diabetic HH patients. Three articles (14, 16, 20) state that there was no improvement at all.
Evaluation of diabetes by means of need for insulin or need for oral hypoglycemic agents was used several times (7, 8, 11, 13, 18). In all of them there is improvement of the diabetes ranging from 30,77% to 45%.
In one article the fasting glucose was taken to evaluate the effect of phlebotomy. In this article there was an improvement in 71,43% of the study population. (9)
Two other articles did not show an improvement in diabetic patients, but they showed an improvement of the glucose metabolism in NGT (15) or IGT (22) patients.
Another article evaluated the effect of phlebotomy in IGT HH patients with a decreased clearance of insulin. (12) They reported a normalisation of the clearance of insulin.
One article reported an improvement in insulin secretion and sensitivity in both NGT and diabetic HH patients. (21)
Two articles evaluated the effect in non-diabetic patients. One stated that HH patients have higher levels of insulin. (10) The other article stated that after phlebotomy insulin secretion increased and insulin sensitivity decreased. (19)

In one article the effect of phlebotomy in high-ferritin DM patients was studied, instead of in diabetic HH patients. They reported improvement of the glucose metabolism. (17)

d) Discussion

The literature search was done only in Medline, no other databases were searched.
It is clear that there is no clear cut answer to our research question. Only a few articles write about the effect of phlebotomy on the glucose metabolism. The sample size of the articles that deal with this problem is usually very small. The largest sample size is 81 patients, the smallest is five. It is difficult to come to a conclusion if the sample size is so small.
In the different articles they use different ways to evaluate the glucose metabolism. Some use only the insulin requirements, other will use an oral glucose tolerance test or laboratory investigations. From that point of view it is difficult to compare the different articles. The treatment of diabetes has evolved over time. The current possibilities for treatment differ a lot from the possibilities 40-50 years ago.
Through the years, we see that several researchers were exploring the effect of phlebotomy on the glucose metabolism in patients with HH. More and more insight in the disease was reached. An important milestone was the discovery of the genetic background of the disease in 1996. Before 1996 a real diagnosis of HH was impossible. It was just a syndrome with some clinical manifestations, that was called HH. We can not be certain that the individuals with HH, are really HH patients. So can we rely on the results of the articles before 1996?

To give an answer to the question if phlebotomy will improve the glucose metabolism, more insight in the pathogenesis of HH, in particular in the pathogenesis of diabetes in HH patients is needed.

Several factors affect the glucose metabolism in patients with HH. It is a very complex and not completely understood mechanism.
Iron plays an interesting role in the glucose metabolism. Fernandez-Real at al (17) evaluated the effect of phlebotomy on glucose metabolism in high-ferritin type two diabetes patients (but without HH) Bloodletting led simultaneously to decreased blood HbA1c and to changes in insulin secretion and insulin resistance. (17) Faccinini FS et al (23) evaluated the effect of phlebotomy in ten healthy blood donors. Four weeks after phlebotomy improved glucose tolerance was observed. So even in non-HH patients phlebotomy can improve glucose metabolism.

Pancreatic beta-cell iron accumulation plays an important role. Cooksey RC et al examined glucose homeostasis and beta-cell function in mouse models of hemochromatosis (with a targeted deletion of the hemochromatosis gene Hfe-/-). They conclude that iron excess results in beta-cell oxidant stress and decreased insulin secretory capacity secondary to beta-cell apoptosis and desensitization of glucose-induced insulin secretion. So iron deposits in the beta-cells will cause apoptosis and loss of insulin secretion capacity via hydroxyl radical formation. (24)
Ramney at al (5) evaluated the glucose homeostasis in iron overloaded hepcidin-deficient mice. These mice presented with heavy pancreatic iron deposits, but only in the acini. The beta-cell function was found unaffected with a normal production and secretion of insulin. The mutant mice were not diabetic, responded as the control group to glucose and insulin challenges, with no alteration of insulin signalling in the muscle and the liver. These results indicate that a decreased

insulin secretory capacity, caused by iron deposits in beta-cells, might trigger diabetes in HH patients. (5) The discussed mouse models are however not suitable to study the pathogenesis of diabetes associated with hemochromatosis.

Besides the beta-cell iron accumulation, the accumulation of iron in the hepatocytes of the liver will play an important role as well. Niederau et al (10) demonstrated that due to accumulation of iron in the hepatocytes, the insulin-extracting capacity of the liver will diminish. In fact this should even improve the glucose metabolism. But liver dysfunction will cause insulin resistance. This may contribute by revealing defects in glucose tolerance. (1)

Several patients with HH and diabetes are overweight and have a high BMI (Body Mass Index). This is of course a well known cause of insulin resistance which can bias our insight in the pathogenesis of diabetes in HH patients.

If we just look to the articles written after 1996, only eight articles are left. Fernandes-Real (17) et al are dealing with high-ferritin type two DM patients. These patients do not have HH. Phlebotomy ameliorates the glucose metabolism. This shows dat iron is interfering with the glucose metabolism. Two articles state that phlebotomy does not give any improvement (20, 16). Two articles state that there is improvement in HH patients with impaired glucose tolerance, but no improvement when DM is already established (15, 22). One article reported an improvement in insulin secretion but a decrease in insulin sensitivity. (19) One article reported an improvement in insulin secretion and sensitivity in both NGT (normal glucose tolerance) and diabetic HH patients (21).
So in general there is improvement of the glucose metabolism, but certainly not in all cases. There is more improvement in patients with impaired glucose tolerance than in patients with already established DM. But the main accent must be on prevention and timely diagnosis of HH. The earlier the diagnosis, the less complications there will be. If diabetes development is prevented completely by early diagnosis of HH, we do not need to answer our research question anymore.

e) Conclusions

Phlebotomy can improve glucose metabolism in less than 50% of the diabetic HH patients. Patients not requiring insulin appear more likely to improve during iron depletion therapy.

f) References

1 Utzschneider KM, Kowdley KV. Hereditary hemochromatosis and diabetes mellitus: implications for clinical practice. Nature Reviews Endocrinology. 6(1):26-33, 2010 Jan.

2 Cassiman D. Hyperferritinemieën en ijzerstapelingsziekten: een klinisch algoritme? Bloedvaten, hart, longen. 2010 Vol 15 Nr 1.

3 Vantyghem MC, Fajardy I, Dhondt F, Girardot C, D'Herbomez M, Danze PM, Rousseaux J, Wemeau JL. Phenotype and HFE genotype in a population with abnormal iron markers recruited from an Endocrinology Department. European Journal of Endocrinology. 154(6):835-41, 2006 Jun.

4 Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Screening for hereditary hemochromatosis: a systemic review for the US. Preventive Services Task Force. Ann Intern. Med. 145:209-223, 2006.

5 Ramey G, Faye A, Durel B, Viollet B, Vaulont S. Iron overload in Hepc1(-/-) mice is not impairing glucose homeostasis. FEBS Letters. 581(5):1053-7, 2007 Mar 6.

6 McClain DA, Abraham D, Rogers J, Brady R, Gault P, Ajioka R, Kushner JP. High prevalence of abnormal glucose homeostasis secondary to decreased insulin secretion in individuals with hereditary haemochromatosis. Diabetologia. 49(7):1661-9, 2006 Jul.

7 Williams R, Smith PM, Spicer EJ, Barry M, Sherlock S. Venesection therapy in idiopathic haemochromatosis. An analysis of 40 treated and 18 untreated patients. Q J Med. 38:1-16, 1969.

8 Dymock IW, Cassar J, Pyke DA, Oakley WG, Williams R. Observations on the pathogenesis, complications and treatment of diabetes in 115 cases of haemochromatosis. American Journal of Medicine. 52(2): 203-10, 1972 Feb.

9 Edwards CQ, Cartwright GE, Skolnick MH, Amos DB. Homozygosity for hemochromatosis: clinical manifestations. Annals of internal medicine. 93:519-252, 1980.

10 Niederau C, Berger M, Stremmel W, Starke A, Stohmeyer G, Ebert R, Siegel E, Creutzfeldt W. Hyperinsulinaemia in non-cirrhotic haemochromatosis: impaired hepatic insulin degradation? Diabetologia. 26(6): 441-4, 1984 Jun.

11 Niederau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and noncirrhotic patients with primary hemochromatosis. N. Engl. J. Med. 313:1256-1262, 1985.

12 Stemmel W, Niederau C, Berger M, Kley HK, Kruskemper HL, Strohmeyer G. Abnormalities in estrogen, androgen, and insulin metabolism in idiopathic hemochromatosis. Annals of the New York Academy of Sciences. 526:209-23, 1988.

13 Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long-term survival in patients with hereditary hemochromatosis. Gastroenterology. 110(4):1107-19, 1996 Apr.

14 Adams PC, Valberg LS. Evolving expression of hereditary hemochromatosis. Semin Liver Dis 16(1):47-54, 1996.

15 Hramiak IM, Finegood DT, Adams PC. Factors affecting glucose tolerance in hereditary hemochromatosis. Clinical & Investigative Medicine – Medicine Clinique et Experimentale. 20(2):110-8, 1997 Apr.

16 Buysschaert M, Paris I, Selvais PH, Hermans MP. Clinical aspects of diabetes secondary to idiopathic haemochromatosis in French-speaking Belgium. Diabetes & Metabolism. 23:308-313, 1997.

17 Fernandez-Real JM, Penarroja G, Castro A, Garcia-Bragado F, Hernandez-Aguado , Ricart W. Blood letting in high-ferritin type 2 diabetes: effects on insulin sensitivity and beta-cell function. Diabetes. 51:1000-1004, 2002.

18 Thielen V, Radermecker RP, Philips JC, Paquot N, Scheen AJ. Hereditary hemochromatosis and diabetes mellitus: diagnostic approach and clinical evolution. Revue Ledicale de Liege. 60(5-6):448-54, 2005 May-Jun.

19 Abraham D, Rogers J, Gault P, Kushner JO, McClain DA. Increased insulin secretory capacity but decreased insulin sensitivity after correction of iron overload by phlebotomy in hereditary haemochromatosis. Diabetologia. 49:2546-2551, 2006.

20 O'Sullivan EP, McDermott JH, Murphy MS, Sen S, Walsh CH. Declining prevalence of diabetes mellitus in hereditary haemochromatosis, the result of earlier diagnosis. Diabetes research and clinical practice. 81:316-320, 2008.

21 Equitani F, Fernandez-Real JM, Menichella G, Koch M, Calvani M, Nobili V, Mingrone G, Manco M. Bloodletting ameliorates insulin sensitivity and secretion in parallel to reducing liver iron in carriers of HFE gene mutations. Diabetes Care. 31:3-8, 2008.

22 Hatunic M, Finucane FM, Norris S, Pacini G, Nolan JJ. Glucose metabolism after normalization of markers of iron overload by venesection in subjects with hereditary hemochromatosis. Metabolism Clinical and Experimental. 59: 1811-1815, 2010.

23 Facchini FS. Effect of phlebotomy on plasma glucose and insulin concentrations. Diabetes Care. 21:2190, 1998.

24 Cooksey RC, Jouihan HA, Ajioka RS, Hazel MW, Jones DL, Kushner JP, McClain DA. Oxidative stress, beta-cell apoptosis and decreased insulin secretory capacity in mouse models of hemochromatosis. Endocrinology. 145:5305-5312, 2004.

3. Project

a) Introduction

In family medicine, diabetes mellitus (DM) is a common disease. We are trained to screen and treat patients in time. We are well aware of the complications and consequences of this disease.

Hereditary hemochromatosis (HH) is not well known. We are less aware of this disease and are unfamiliar with the complications. There are no clear guidelines in family medicine. Most of the time it is not clear who is doing the follow-up of these patients: the specialist or the family doctor?

In Europe the genetic prevalence is about one per 200-250 individuals. This means that a family doctor with approximately 1000 patients, will have four to five patients who are genetically susceptible to develop iron overload. 80-85% of typical HH patients are homozygote for the C282Y-mutation. Phenotypic expression only occurs in approximately 70% of C282Y homozygotes. Only 10% of C282Y homozygotes will develop severe iron overload accompanied by organ damage and clinical manifestations such as fatigue, lethargy, hepatomegaly, diabetes, arthralgias, congestive heart failure or cirrhosis. The reasons for this low phenotypic penetrance are unknown. (25) We can not predict which of these genetically susceptible patients will become symptomatic. Once symptomatic the burden of HH is high. Only few symptoms are reversible. As written in our literature research, phlebotomy will ameliorate the glucose metabolism in fewer than 50% of the cases. Prevention of organ damage by timely diagnosis of HH remains the most important step in the treatment of HH. Early diagnosis and phlebotomy can prevent the development of tissue damage, reducing morbidity and mortality. This will lead to a long-term survival similar to the general population. (26) The prognosis of HH is determined by the presence of cirrhosis and hepatocellular carcinoma. (27) So we can state that the screening, care and follow-up of these patients, especially in family medicine, needs to be improved.

The diagnosis of HH is suggested by elevated serum ferritin (F) levels and/or elevated transferrin saturation (TS) levels. The diagnosis is confirmed by genetic testing.
Serum F levels correlate with the degree of body iron stores but it has a significant false positive rate because of elevations related to inflammation. F can also be elevated in patients with necro-inflammatory liver disease (alcoholic liver disease, chronic hepatitis B and C, nonalcoholic fatty liver disease), in lymphomas and other malignancies, and in patients with other nonhepatic chronic inflammatory conditions. In these patients, F levels do not correlate with the body iron stores. (25)

TS is calculated from the ratio of serum iron to total iron-binding capacity. It is advisable to confirm an elevated TS with a second determination on a fasting specimen. A cutoff value of 45% is often used because of its high sensitivity for detecting C282Y homozygotes. But is has a lower specificity and positive predictive value compared to higher cutoff values. So with a cutoff value of 45% we will also identify persons with minor secondary iron overload as well as some C282Y/wild-type heterozygotes. (25)
But F and TS are both useful to determine. A variety of disease conditions unrelated to iron overload may cause a nonspecific rise in serum F and in the absence of elevated TS, this rise may be nonspecific. Conversely, iron overload may be present in a patient with an elevated F and a normal TS (particularly in non-HFE-related iron overload or in a C282Y/H63D compound heterozygote). (25)
Figure B shows an algorithm regarding testing and treatment for HH.

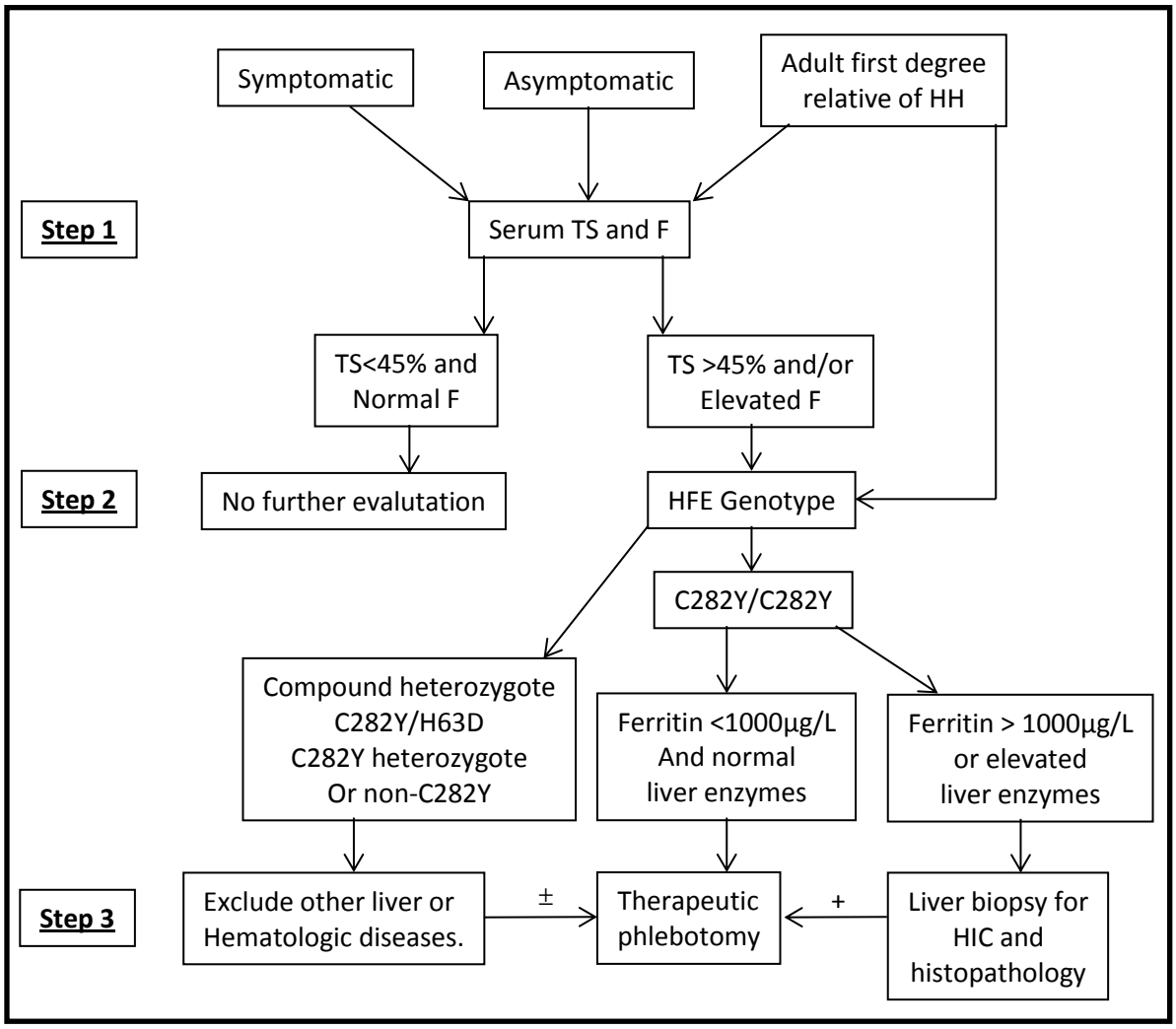

Figure B: algorithm regarding testing and treatment for HH, according to AASLD guidelines.
HH: hemochromatosis;TS: transferrrin saturation; F: ferritin; HIC: hepatic iron content

Screening should be done in symptomatic patients and first degree relatives of HH patients. There are also certain risk groups that should be targeted for evaluation: suspected organ involvement and those with chance detection of biochemical and/or radiological abnormalities suggestive of iron overload. (25) Patients with abnormal liver function and diabetes (organ involvement) are considered as target groups.
Diabetes is a common complication of HH. But are we considering that a new diabetic case could be iron-induced? Aren't we missing the diagnosis of iron-induced diabetes?

With this project we want to obtain the following information:

1. Are the screening goals for HH in diabetic patients reached in family medicine ('De Drempel' and Intego-database) and in an academic hospital (University Hospital of Leuven)?
2. Is genetic testing done and are the indications for genetic testing correct in family medicine ('De Drempel and Intego-database) and in an academic hospital (University Hospital of Leuven)?

b) Methods

We wanted to compare the data from 3 different sources:

- A general practice (De Drempel)
- An epidemiological network of general practices (Intego)
- An academic hospital (University Hospital of Leuven (UH Leuven))

A population born between 1941 and 1966 was selected. All patients with diabetes mellitus type two (DM) were selected. For these DM patients their medical file was opened, and laboratory results were searched. All ferritin (F) and transferrin (TS) saturation values were collected and analysed.

I did myself the data collection for all patients of the general practice 'De Drempel'. A total of 2602 patients born between 1941 and 1966 was found. Occasional patients were excluded by GMD (globaal medisch dossier). Only patients who had their GMD in 2011 or 2012 in the general practice 'De Drempel', were admitted to the study. 1385 patients met these criteria and 1217 were excluded. The data were collected between june 2012 and august 2012.
As medical software we use 'Health One' . For our research we made a new grid analysis for HH which contained: fasting glucose, postprandial glucose, HbA1c, iron, ferritin, transferrin saturation, transferrin, weight and length. The grid analysis showed all results available in the patients file over time. The most recent values were taken.
For each of the 1385 selected patients the file was opened and the grid analysis was done.
Diabetes mellitus was suspected in cases with fasting glucose above 126 mg/dL and postprandial glucose above 200 mg/dL. HbA1c, if available was considered abnormal above 6,0%. The diagnosis of DM was confirmed with medication (insulin, glucophage, …) or the diagnosis written on the problem list of the patient.
For women a ferritin value above 300µg/L and for men a ferritin value above 400µg/L was used as a cutoff value.
A transferrin saturation ≥45% was considered abnormal.
The diagnosis of hemochromatosis was confirmed if the diagnosis was written on the problem list in the patients file. The file was checked for specialists reports to confirm the diagnosis. A protocol with genetic testing was searched as well. Finally I checked as well if phlebotomies were done.
The general practice 'De Drempel' is a group practice with five family doctors (VS, BM, MH, JS, ML). Two of these five doctors are training new family doctors. A trainee doctor is also joining the general practice.

The results from the intego-database were collected by the Intego team from Prof. Dr. S. Bartholomeeusen.

The results from the university hospital in Leuven were collected by Annick Vanclooster. She is doing research for the Hepatology department from Prof. Dr. D. Cassiman.

c) Results

Results of group practice 'De Drempel', Lommel

A total of 1385 patients participated in our study. 106 out of these patients have diabetes type two. This is 7,65% of the study population.
Four patients of our total study group are known with HH. They were already on treatment, their F and TS values are more or less normal. One of them is also a known diabetic. He was only recently (2011) diagnosed with HH and diabetes. The diabetes was already present at the time of HH diagnosis. Genetic testing showed a homozygous C282Y mutation. The follow-up of this patient is done by the gastro-enterologist and endocrinologist, who confirmed the diagnosis. Phlebotomies are done in hospital setting. (Patient 2 in Table 3)
For patient one in table three the diagnosis of HH was made before 1996, this is before genetic testing was introduced. In the patients problem list HH was written and several specialist protocols stated that he was a HH patient. Phlebotomies were done regularly in the general practice 'De Drempel'.
Patient three shows a homozygous C187G mutation. Patient four shows a homozygous C282Y mutation. Both of them receive regularly phlebotomies in the general practice 'De Drempel'. For patient four hemoglobin, iron and F were checked in between the phlebotomies. A recent TS value was not found. At time of diagnosis she had a TS of 102%, but no other values were available in the file. (Table 3)

	Date of birth	Gender	Ferritin	Transferrin saturation	Known diabetes?	HH mutation
1	26/09/1944	M	159	53%	No	Diagnosis before 1996
2	21/10/1945	M	20	14%	Yes	C282Y+/+
3	15/09/1946	M	67	54%	No	C187G+/+
4	23/08/1965	V	64	?	No	C282Y+/+

Table 3: Known HH patients

In 'De Drempel' we have 106 diabetic patients. In eight patients we do not have F values nor TS values available, this is 7,55%.
In 98 patients at least one parameters is known. In 80 patients TS is lacking, this is 75,47%.
13 patients have both normal F and normal TS values. This is 12,26%. One patients of these 13 is a known HH patient on treatment. His values are normal. (Patient 2 in Table 3)
Five patients have abnormal results, this is 4,72%. Two patients have a raised F value but the TS is unknown. In three patients there is a raised F value but a normal TS value. (Figure C) In none of the patients with abnormal results genetic testing was done.

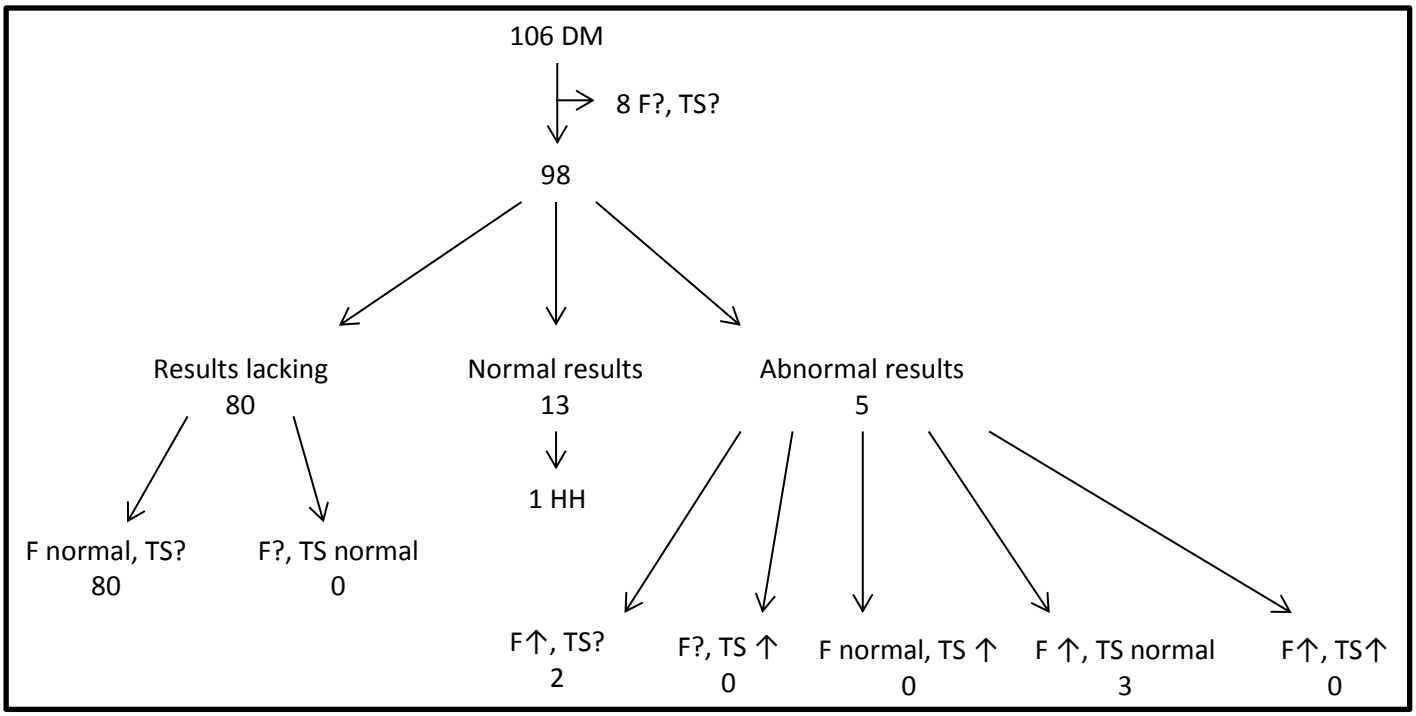

Figure C: Results from 'De Drempel'
DM: diabetes mellitus type 2; F: ferritin; TS: transferrin saturation; HH: hemochromatosis

Table four (see appendix 2) shows the distribution of the 106 patients among the five doctors of general practice 'De Drempel'. The patient was allocated to one doctor if the follow-up was done by this doctor and/or the GMD of the patient was written on the doctor's name.

VS has 25 DM patients. In all patients the F values were known. In most of the patients (22) the F values were determined on regular basis. In three patients the TS value was known as well. Three other patients had F values that were raised one or two times, the rest of their F values were normal.

BM has 15 DM patients in the study. The TS was never available. In one patient F nor TS values were available. Two patients had one or two times a raised F value, the rest of their values were normal. One patient has a F value that is always raised.

MH has 12 DM patients. One patient has no values available. TS is never available.

JS has 25 DM patients. In five patients no values are available. TS is known in four patients. In 15 patients F values were available less than three times. In five patients F was determined regularly, two of them had an episode of raised values.

ML has 29 DM patients. F values were always available. In five patients TS was known as well. One patient had an episode of one or two raised F values. One patient has always raised F values, but the TS is normal. One patient is a known HH.

Results from the Intego-database

This research was done by the team of the Intego-database (Prof. Dr. Bartholomeeusen S.)
In 2011 a total of 2784 diabetic patients are known in the Intego-database. In 646 patients no iron parameters were known, this is 23,20%.
If we focus on the 2138 patients of whom we have values available, some results are lacking in 1337 patients, this is 48,02%. In 1320 of these patients the F value is normal, but no TS is known. In 17 patients the F value is unknown and the TS is normal.
In 630 patients both F and TS values are known and normal. This is 22,63%.
In 171 patients we have abnormal results. This is 6,15%. In 89 patients the F is raised but the TS is unknown. In one patient the F is unknown and the TS is raised. In 21 patients the F is normal and the TS is raised. In 48 patients the F is raised and the TS is normal. In 12 patients both F and TS are raised. None of the patients were diagnosed with HH. But we do not have any information about the genetic testing. (Figure D)
In 2073 patients (646 F? TS? + 1320 F normal TS? + 17 F? TS normal + 89 F↑ TS? + 1 F? TS↑) parameters are lacking. This is 74,46%.

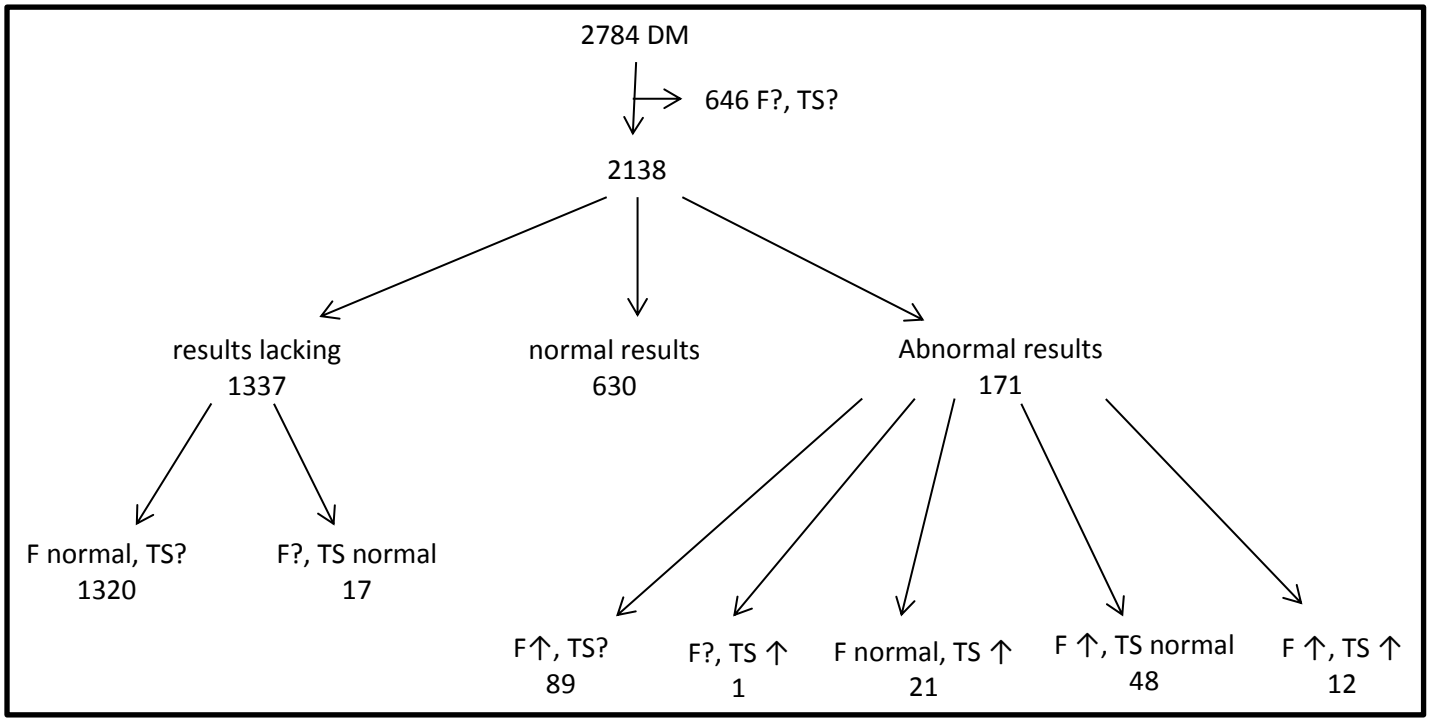

Figure D: Results from the Intego-Database
DM: diabetes mellitus type 2, F: ferritin; TS: transferrin saturation

Results from University Hospital Leuven

This research was done by Annick Vanclooster. She is doing research for the hepatology department at the University Hospital in Leuven.

A total of 1457 known diabetic patients were selected in 2011. In 395 patients the F, nor the TS was known, this is 27,11% of the group. In 939 both values of F and TS values are normal, this is 64,44% of all the patients.
In 123 patients there were abnormal values, this is 8,44% of all patients.
If we focus on this group of 123 patients, we see that in four patients, only the F was known, and no value of TS could be found in the file. All of these four patients had a raised F, this is 3,25% of the group with abnormal values. In none of these four patients further genetic testing was done for HH.
In two patients, the F value was normal, but the TS value was raised. This is 1,62%. One patient was never genetically tested, the other patient had a HH negative result.
In 90 patients (=73,17%), the F value was raised and the TS normal. 86 patients out of those 90 were never genetically tested for HH. In four of these 90 patients genetic testing for HH was done. Three of them had a negative result. One patient showed a C282Y/- mutation.
In 27 patients (= 21,95%) both F and TS values were raised. 18 of them were never genetically tested for HH. In nine patients further genetic testing was done. Six of them showed no HH. Two of them showed a C282Y/- mutation. One patient showed the C282Y/H63D mutation. (Figure E) We can conclude that in 395 patients both parameters are lacking. In 123 patients at least one value is raised. Genetic testing was only done in 15 of these cases. 108 patients with abnormal values were never genetically tested.

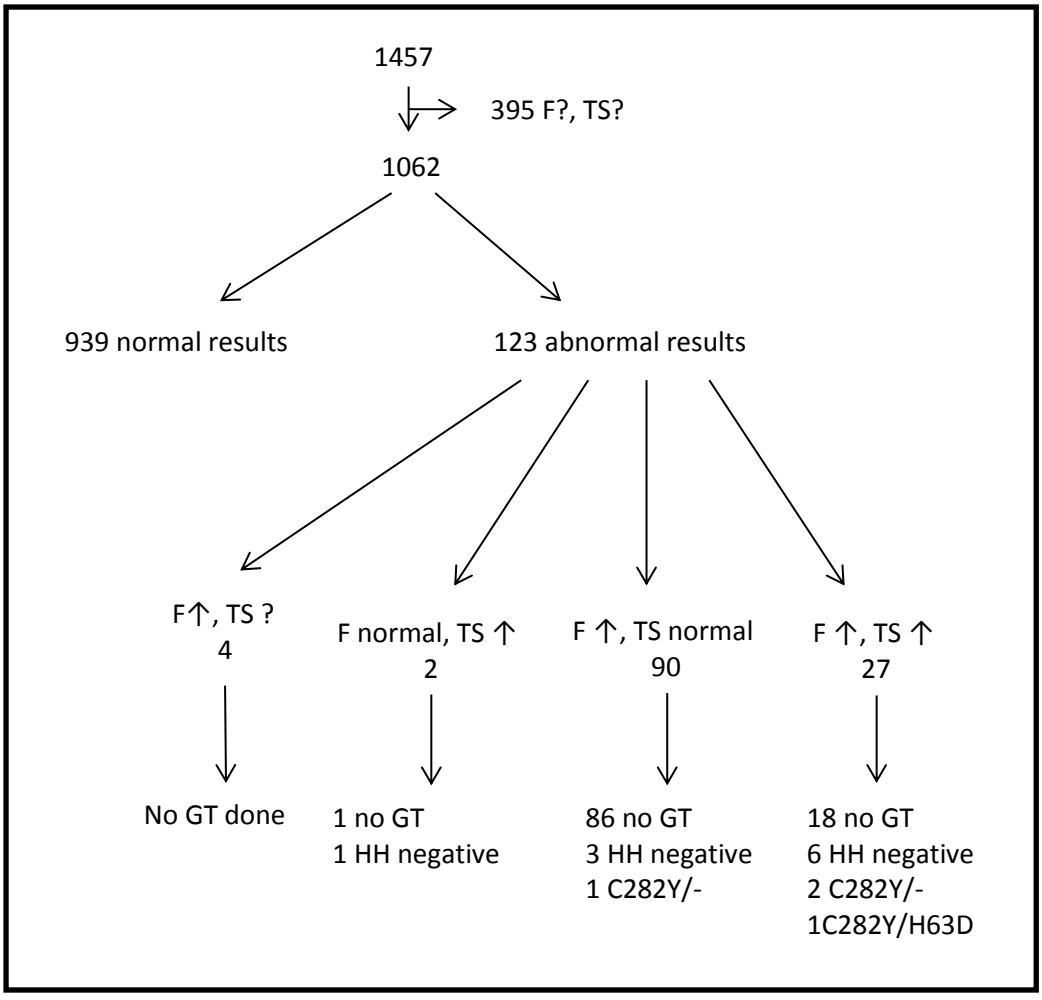

Figure E: results from the University Hospital Leuven
F: ferritin; TS: transferrin saturation; GT: genetic testing; HH: hemochromatosis

Table five compares the availability of results between the three databases. If we look at the group of patients with no known iron values (F?, TS?) at all, 'De Drempel' is showing 7,55%, Intego 23,20% and UH Leuven 27,11%
In the group with both values known and normal it is 12,26% for 'De Drempel', 22,63% for Intego and 64,45% for UH Leuven.
In the group with one value lacking (F or TS) it is 75,47% for 'De Drempel' and 48,03% for Intego. UH Leuven has no patients in this group.
In the group with abnormal results 'De Drempel' is showing 4,72%, Intego 6,14% and UH Leuven 8,44%.

	De Drempel	**Intego**	**UH Leuven**
F? TS?	7,55%	23,20%	27,11%
F normal, TS normal	12,26%	22,63%	64,45%
F or TS lacking	75,47%	48,03%	0
Abnormal results	4,72%	6,14%	8,44%

Table 5: Availability of results in the three databases.

Table six compares the three databases based on lacking results in detail. In UH Leuven in 72,62% of the patients both F and TS are known. For 'De Drempel' this is 15,09% and for Intego 25,54%.
One parameter is known in 77,36% of the patients of 'De drempel, in 51,26% (0,65% + 50,61%) of the patients of Intego and 0,27% of the patients in UH Leuven. The group with both F and TS lacking was also seen in table five.

	De Drempel		**Intego**		**UH Leuven**	
DM patients = n	106		2784		1457	
F known, TS Known	16	15,09%	711	25,54%	1058	72,62%
F↑, TS↑	0		12 (=1,69%)		27 (=2,55%)	
F nl, TS↑	0		21 (=2,95%)		2 (=0,19%)	
F↑, TS nl	3 (=18,75%)		48 (6,75%)		90 (=8,51%)	
F nl, TS nl	13 (=81,25%)		630 (=88,61%)		939 (=88,75%)	
F unknown, TS known	0		18	0,65%	0	
TS↑, F?	/		1 (=5,56%)		/	
TS nl, F?	/		17 (=94,44%)		/	
F known, TS unknown	82	77,36	1409	50,61%	4	0,27%
F↑, TS?	2 (=2,44%)		89 (=6,32%)		4 (=100%)	
F nl, TS?	80 (=97,56%)		1320 (=93,68%)		0	
F unknown, TS unknown	8	7,55%	646	23,20%	395	27,11%

Table 6: Distribution of available results in the three databases.

d) Discussion

In the group practice 'De Drempel' we have a total of 2602 patients born between 1941 and 1966. But only 1385 patients were selected based on their GMD. We can already identify a possible bias: whether patients have their GMD in our practice or not depends on the doctor in charge. Some of my colleagues are very strict and renew the GMD on the first visit of the patient in the beginning of the year. Others are less strict and will renew the GMD only when they think about it. To minimise this effect patients with a GMD in 2011 and in 2012 were selected.
A second bias in the results is the time between the moment we decided to do this research and the moment the values were collected. In December 2011 we decided to do this research. The data were collected from June to August 2012. As my colleagues knew the purpose of my research, they could have done more lab tests (including F and TS) during a period of six months. All results were checked again in October 2012. In two patients allocated to JS, the F value was taken for the first time during the follow-up of the patient in the period of six months between December 2011 and May 2012.

Four patients of the total population of 'De Drempel' were known with HH. They were already on treatment (phlebotomy). As a result their F values are all normal. The TS is not normal in all cases. The diagnosis can be considered as confirmed in only two patients with the C282Y+/+ mutation. (See Table 3) In one patient the diagnosis was done before 1996. For this patient we cannot be sure of the diagnosis. One patient has the C187G+/+ mutation. The relevance of this mutation is still uncertain especially when homozygous.

Table five (see above) compares the availability of results between the three databases. If we look at the group of patients with no iron values (F and TS) at all, we see that 'De Drempel' is showing the best results. In 7,55% of the patients no values are known. Intego and UH Leuven are doing worse with 23,20% and 27,11% each.
If we look at the group of patients with both normal F and normal TS values, we see that UH Leuven is having the best percentage: 64,45%. 'De Drempel' and Intego have much lower results: 12,26% and 22,63%. But of course this percentage depends on how many values that are lacking. In 'De Drempel' 75,47% of the patients have only one parameter recorded, which explains the low percentage of 12,26% in the group with known normal ferritin and transferrin saturation. In the Intego-database we see the same problem. In 48,03% of the patients only one parameter is known, which explains the low percentage of 22,63% with both normal parameters. In UH Leuven there is no group with lacking results.
When we look at the abnormal results we see quite similar results in all groups: 4,72%, 6,14% and 8,44%. Tabel seven is showing the abnormal results in detail.

		De Drempel	Intego	UH Leuven
1	**F↑, TS?**	1,89%	3,20%	0,27%
2	**F?, TS↑**	0	0,04%	0
3	**F normal, TS↑**	0	0,75%	0,14%
4	**F↑, TS normal**	2,83%	1,72%	6,18%
5	**F↑, TS↑**	0	0,43%	1,85%

Table 7: Abnormal results in detail.

In the first two groups (1 and 2) we have a raised value but the other value is lacking (F↑, TS? or F?, TS↑). In fact this percentage can be counted together with the group of lacking results (Table 5). This gives the following results: De Drempel 77,36%, Intego 51,26% and UH Leuven 0,27%.
In all five groups of abnormal results genetic testing should have been done. In 'De Drempel' and Intego no genetic testing was done in these cases. In UH Leuven genetic testing was done in 14 cases out of the 123 cases with abnormal results. This is 11,38%.
So we can conclude that the University Hospital shows the best results of having both parameters recorded. Group practice 'De Drempel' is having the most patients with known F values and has the least patients with none of the parameters known.
Of course we have to consider the sample size. Group practice 'De drempel' is having the smallest sample size (n= 106). So the results are less reliable than the results of the Intego-database (n=2784) and of the University Hospital of Leuven (n=1457).

Table four (see appendix 2) shows the distribution of the patients among the different doctors in 'De Drempel'. A difference was made between patients with more than three F values (F regularly) and patients with less than three ferritin values. For MH and JS ferritin was not regularly measured in 41,67% and 60,00% of their patients respectively. VS, BM and ML are doing better with 12,00%, 6,67% and 10,34% respectively. In 16,67% of the patients of MH and 20% of the patients of JS F nor TS values are known. We can conclude that MH and JS are not determing iron values (ferritin) on a regular basis.
VS, BM and ML are including ferritin in their general check-up laboratory investigations.
TS is done only in 16 out of the 106 DM patients in de 'De Drempel'. In general practice TS is only done in specific conditions such as a raised ferritin value.

If we look to table six (see above), UH Leuven stand out with 72,62% of the patients with both F and TS known. Both parameters are lacking in 7,55% of 'De Drempel, 23,20% of Intego and 27,11% of UH Leuven. One parameter is only known in 77,36% of 'De Drempel', 51,26%(0,65%+50,61%) in Intego and 0,27% in UH Leuven.
It doesn't come to a surprise that in the university hospital of Leuven ferritin and transferrin saturation are usually known at the same time. Transferrin saturation is considered as a step-further investigation. At a third level hospital this test is done more easily than on the level of family medicine. Ferritin and transferrin saturation are more often done together.

e) <u>Conclusion</u>

In conclusion we can state that both in general medicine and in a third line hospital F and TS are not determined on a regular basis in diabetic patients. Both parameters are lacking in 7,55 to 27,11% of the diabetic patients. In general medicine F is often taken on a regular basis but TS is hardly determined. In a third line hospital, if taken, F and TS are usually taken together.
Genetic testing is hardly done in both general medicine and third line hospital. The screening goals for HH in diabetic patients are not met.

f) References

25 Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American association for the study of liver diseases. Hepatology 54(1):328-343, 2011.

26 Janssen MCH, Swinkels DW. Hereditary haemochromatosis. Best Practice & Research Clinical Gastroenterology. 23:171-183, 2009.

27 Heggermont W, De Rudder P, Cassiman D, Decallonne B. Hereditaire hemochromatose als oorzaak van diabetes mellitus. Tijdschrift voor Geneeskunde. 66(12): 593-600, 2010.

4. Abstract

Hereditary hemochromatosis and iron-induced diabetes: a missed diagnosis?

Haio: De Bolle Sarah
Universiteit: KULeuven
Promotor: Prof. Dr. Aertgeerts Bert
Co-promotor: Prof. Dr. Cassiman David, Annick Vanclooster
Praktijkopleider: Dr. Jan Swinnen, Dr. Martin Lagrain

Context/Context: Hereditary hemochromatosis (HH) is a genetic disorder, that can lead to unregulated absorption of iron with resultant iron overload. The accumulation of iron in the entire body will eventually lead to fibrosis, cirrhosis, diabetes,… wich will lead to a higher morbidity and mortality. This can be prevented completely by timely diagnosis and treatment (phlebotomy). In family medicine we are less aware of HH and are unfamiliar with the complications, although the genetic prevalence is about one per 200-250 individuals. Diabetes mellitus is a common disease and we are trained to screen and treat patients in time. But are we considering diabetes as a common complication of HH?

Onderzoeksvraag/Research question: In our literature research we want to investigate if phlebotomy has an effect on the glucose metabolism in diabetic HH patients. Can phlebotomy ameliorate the glucose metabolism in these patients? With our project we want to investigate if the screening goals for HH in diabetic patients are reached in family medicine and in an academic hospital. And we want to know if genetic testing is done and if the indications for genetic testing are correct in family medicine and in an academic hospital.

Methode (literatuur & registratiewijze)/Methods: We conducted a systematic literature research in the database MEDLINE with the search filter OVID from 18/05/2012 till 18/06/2012. As search terms, hemochromatosis, phlebotomy, bloodletting, iron overload, diabetes mellitus, hyperglycemia and hyperinsulinism were used. For our project we wanted to compare the data from three different sources: a general practice (‘De Drempel), an epidemiological network of general practices (Intego), and an academic hospital (UH Leuven). A population born between 1941 and 1966 was selected. All patients with diabetes mellitus type two were selected. Their medical file was searched for ferritin (F) and transferrin saturation (TS) values, and if genetic testing for HH was ever done.

Resultaten/Results: In our literature research we found 16 articles dealing with the effect of phlebotomy on the glucose metabolism in diabetic HH patients. Only few articles report some improvement of the glucose metabolism. Less advanced stages of diabetes will show more improvement. In our project both F and TS values were lacking in 7,55%-23,20%-27,11% (De Drempel – Intego – UH Leuven). Both parameters were known in 15,09%-25,54%-72,62%. Genetic testing was only done in UH Leuven, in 11,38% of the patients with abnormal results.

Conclusies/Conclusion: Plebotomy can improve glucose metabolism in less than 50% of the diabetic HH patients. Patients not requiring insulin appear more likely to improve during iron depletion therapy. F and TS are not determined on a regular basis in diabetic patients in both general medicine and a third line hospital. Both parameters are lacking in 7,54 to 27,11% of the patients. In general medicine F is taken regularly but TS is hardly ever determined. In a third line hospital F and TS are usually taken together. Genetic testing is hardly done in both general medicine and third line hospital. The screening goals for HH in diabetic patients are not met.

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5. Votes of thanks

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Special thanks to my husband Elie Vromman for reading and re-reading all my writings.

6. Appendix

Appendix 1: Details of 106 diabetic patients of 'De Drempel'.

Date of birth	Gender	Ferritin	Transferrin-saturation	Genetic testing done?	Doctor
27/08/1941	F	47	?	No	MH
10/11/1941	M	179	?	No	VS
25/09/1941	M	100	?	No	VS
27/06/1941	F	5	4%	No	JS
28/09/1941	M	72	?	No	JS
14/12/1941	M	233	?	No	JS
05/07/1942	M	138	?	No	BM
07/11/1942	F	138	?	No	JS
02/03/1942	F	**333**	?	No	JS
18/04/1943	M	?	?	No	JS
15/01/1943	F	128	?	No	MH
01/02/1943	M	21	?	No	VS
11/02/1943	F	132	?	No	JS
17/08/1943	M	119	?	No	BM
24/01/1943	M	77	11%	No	ML
18/08/1943	F	85	?	No	ML
02/06/1943	M	208	?	No	ML
21/02/1943	F	142	?	No	ML
30/01/1944	F	46	?	No	VS
18/02/1944	F	46	?	No	VS
03/12/1944	M	331	32%	No	JS
05/08/1944	M	75	?	No	BM
09/11/1944	F	32	?	No	VS
30/06/1944	F	45	?	No	MH
21/12/1945	M	196	21%	No	JS
01/09/1945	M	105	?	No	BM
12/03/1945	M	258	?	No	VS
29/08/1945	F	127	?	No	MH
27/12/1945	M	113	?	No	JS
02/10/1945	M	?	?	No	JS
25/03/1945	M	95	?	No	JS
28/06/1945	M	30	?	No	ML
15/12/1945	F	**378**	23%	No	ML
21/10/1945	**M**	**20**	**14%**	**Yes**	**ML**
26/12/1946	F	91	?	No	ML
17/07/1946	M	51	19%	No	VS
22/02/1946	F	88	?	No	BM
30/07/1946	F	?	?	No	MH
01/07/1946	M	127	?	No	VS
31/05/1946	M	37	?	No	ML
01/03/1947	F	32	?	No	MH
30/05/1947	M	248	?	No	ML
22/10/1947	M	**563**	?	No	BM

28/10/1947	M	245	?	No	MH
13/10/1947	F	20	?	No	ML
19/10/1947	M	**689**	34%	No	ML
05/03/1948	F	96	?	No	JS
18/04/1948	M	181	?	No	VS
29/03/1948	M	?	?	No	MH
04/03/1948	M	117	?	No	JS
20/03/1948	M	146	?	No	ML
02/05/1949	M	87	?	No	JS
30/03/1949	M	103	15%	No	VS
25/08/1949	F	196	?	No	ML
12/01/1949	F	55	?	No	BM
31/12/1950	F	138	?	No	ML
01/06/1950	F	198	?	No	MH
18/12/1950	M	135	?	No	VS
18/11/1950	M	?	?	No	JS
12/05/1950	M	99	?	No	BM
26/10/1950	M	324	?	No	JS
01/06/1951	M	22	?	No	ML
01/05/1951	F	143	?	No	VS
27/02/1951	F	54	?	No	ML
02/09/1952	F	91	28%	No	ML
19/01/1952	M	?	?	No	JS
24/05/1952	M	122	?	No	ML
15/11/1952	M	152	?	No	JS
10/08/1952	F	167	?	No	VS
24/07/1952	F	77	?	No	MH
08/08/1952	F	**305**	26%	No	VS
23/08/1952	M	99	?	No	VS
27/05/1952	M	182	?	No	BM
24/09/1953	M	278	?	No	ML
12/05/1953	M	35	18%	No	ML
09/01/1953	M	155	?	No	ML
09/11/1953	M	54	?	No	VS
22/09/1953	F	163	?	No	BM
07/07/1955	M	47	?	No	MH
18/08/1955	M	41	?	No	ML
19/12/1955	M	27	?	No	MH
25/01/1956	M	221	?	No	JS
17/01/1956	M	50	?	No	VS
28/08/1956	F	60	?	No	VS
29/09/1956	M	219	?	No	BM
01/01/1957	M	149	?	No	JS
19/12/1957	M	142	?	No	JS
27/12/1957	M	?	?	No	JS
01/05/1958	F	65	?	No	VS
12/12/1958	M	125	?	No	ML
25/12/1958	F	181	25%	No	ML
01/01/1959	M	272	?	No	VS
18/05/1959	M	113	?	No	ML

11/07/1960	M	18	?	No	VS
21/10/1960	F	73	?	No	VS
28/11/1960	F	142	18%	No	JS
28/04/1961	M	228	?	No	ML
18/06/1961	M	93	37%	No	ML
22/09/1961	M	140	?	No	BM
01/01/1962	M	128	?	No	JS
06/08/1963	M	206	?	No	VS
19/08/1963	F	26	?	No	BM
06/09/1964	M	?	?	No	BM
13/03/1965	F	93	20%	No	ML
20/05/1965	M	238	?	No	BM
21/09/1965	F	138	?	No	VS

Appendix 2: Distribution of patients among the five doctors of ‘De Drempel’ (Table four).

	VS	**BM**	**MH**	**JS**	**ML**	**Total**
F? TS?	/	1	2	5	/	**8**
F regularly normal, TS?	16	10	5	1	19	**51**
F<3 known values, TS?	3	1	5	13	3	**25**
F regularly normal, TS normal	3	/	/	1	4	**8**
F<3 known values, TS normal	/	/	/	2	/	**2**
F 1-2x ↑, rest normal, TS?	3	2	/	2	1	**8**
F 1-2x↑, rest normal,TS normal	/	/	/	1	/	**1**
F always ↑ TS?	/	1	/	/	/	**1**
F always ↑, TS normal	/	/	/	/	1	**1**
HH	/	/	/	/	1	**1**
Total	**25**	**15**	**12**	**25**	**29**	**106**

Table 4: Distribution of patients among the 5 doctors of ‘De Drempel’.