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Sommaire

Influence of obesity-susceptibility loci (MC4R and INSIG2) on the outcome of weight loss and amelioration of co-morbidity in obese patients treated by a gastric-bypass

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Abstract:

BACKGROUND: Genome-wide association and linkage studies have identified multiple susceptibility loci for obesity.

OBJECTIVE: We hypothesized that such loci may affect weight loss and co-morbidity amelioration outcomes following a gastric-bypass.

DESIGN: A total of 200 obese patients who underwent a gastric bypass surgery were genotyped for single-nucleotide polymorphisms (SNPs) in insulin induced gene 2 (INSIG2) and melanocortin 4 receptor (MC4R) obesity genes.

RESULTS: After a follow-up of 18 month, the patients (192) data of weight excess loss (72 %) and co-morbidities (Hypertension -62- and Diabetes -39-) were analyzed and compared. 26 Patients with SNP were found (9 MC4R and 17 INSIG2). No significant differences in weight excess loss and amelioration of co-morbidities were revealed.

CONCLUSIONS: The data suggest no influence of weight excess loss and amelioration of co-morbidities after gastric-bypass by genetic susceptibility.

INTRODUCTION

Obesity is the most common nutritional problem in the western countries and is growing rapidly. It is a major public health problem of the twenty first century due to the higher mortality in obese patients and comorbid physical conditions that produces; hypertension, dyslipidemia, diabetes mellitus and cardiovascular diseases are the main diseases that are linked to morbid obesity [1].

Despite the change of eating habits and reduced physical activity may partly explain the increasing prevalence of obesity, there is a clear genetic contribution to the regulation of body weight [2].

The most common form of familial obesity is associated with mutations of melanocortin 4 receptor gene (*MC4R*) [3] while autosomal recessive disorders include leptin deficiency (MIM 164160), leptin receptor deficiency (MIM 601007), prohormone convertase-1 deficiency (MIM 600955), and proopiomelanocortin deficiency (MIM609734). *MC4R* is a 332 amino acid protein encoded by a single exon gene localized on chromosome 18q22 [4,5]. *MC4R* belongs to the family of 7-transmembrane G-protein linked receptors and signals through activation of adenylate cyclase[1]. More than 70 mutations have been identified so far in *MC4R* gene. Clinically, children heterozygous for a pathogenic *MC4R* mutation as well as having an increase in body fat have also lean body mass. The linear growth of these subjects is impressive; *MC4R* mutation carriers have usually a height standard deviation of + 2 compared to the standard population and other obese children. Additionally, probands have higher levels of fasting insulin and are objectively hyperphagic[6].

There are also many major obesity susceptibility loci, especially the *INSIG2* gene mapped on chromosome 2q14.1. This gene, together with a second member of the same family (*INSIG1*) encodes closely related proteins of the endoplasmic reticulum that block proteolytic activation of sterol regulatory element-binding proteins and membrane bound transcription factors that activate synthesis of cholesterol and fatty acids in animal cells. These proteins also restrict lipogenesis in mature adipocytes and block differentiation of preadipocytes [7-9]. Recently, a single nucleotide polymorphism (SNP) located about 10 kb upstream of *INSIG2* (rs7566605) was shown to be associated with an increased obesity risk for CC homozygotes in a cross sectional study of adults and childrens[10].

Our purpose was to investigate the relevance of the *MC4R* gene and SNPrs7566605 in a cohort of morbid obesity patients selected for laparoscopic gastric by-pass and analyze the behaviour of patients with mutated genotype as regards the postoperative weight loss and changes in comorbidities associated.

KEY WORDS: MC4R gene, INSIG2 gene, morbid obesity, laparoscopic gastric bypass, mutated genotype, postoperative weight loos, improve comorbidities

METHODS

Patients and materials

This study group consisted of 195 patients who underwent to laparoscopic gastric by-pass for morbid obesity. All patients underwent a standardized pre-operative study in collaboration with an endocrinologist, a psychiatrist and a dietician. Laboratory test were performed to determine the pre-operative levels of cholesterol, triglycerides, glycated hemoglobin. All patients underwent to laparoscopic gastric by pass with a transmesocolic retro-gastric technique.

Additionally, we investigated the weight loss curve of the global population after gastric by-pass by excess weight loss(EWL). Were analyzed pre and post-operative values of cholesterol, triglycerides, glycated haemoglobin. Furthermore, we recorded and analyzed the amount of insulin, oral antidiabetic and antihypertensive recruited before and after surgery. All results were analyzed first globally, and then separately compared between the *MC4R* and *INSIG2* carriers and non carriers, and subsequently the same was done by taking into account each gene mutation separately. Statistical analysis was performed using the $\chi 2$ test and taking as threshold of statistical significance $p<0,05$.

Informed consent was obtained from all individuals for sample collection and molecular analysis, and human studies were approved by local or national ethical review board. Genomic DNA isolated from peripheral leukocytes was used for direct sequencing and pyrosequencing analyses.

MC4R mutation analysis

Mutation analysis was performed by PCR amplification and direct sequencing of exons and flanking intronic sequences of the *MC4R* gene. Primers were designed to give a maximum product size of 500 bp and a minimum of 40 bp flanking the splice sites, by use of PRIMER3 program. From each sample, 20 ng of DNA was amplified in a 10-µl PCR by use of AmpliTaq Gold (Perkin Elmer Applied Biosystems®, Foster City, CA). Bidirectional sequencing was performed using both of the M13 primers and BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) (Perkin Elmer Applied Biosystems®, Foster City, CA), and separation was done on a 3130xl DNA Analyzer (Perkin Elmer Applied Biosystems®, Foster City, CA). Base calling, quality assessment, and assembly were performed using the Phred and PolyPhred software suite. To filter out low-quality sequence, only sequences that had a Phred score 27 were included in the analysis. To minimize false-negative results, every low-quality read was visually examined for indels. All sequence variants identified were verified by manual inspection of the chromatograms.

Pyrosequencing

Here, the SNP rs7566605 in the vicinity of *INSIG2* was genotyped by sensitive pyrosequencing method. The three primers were the following: 5'-TCAACCGAGAGATGAAGGAAA-3' (forward primer), 5'-AAGCCAGCCATAAGCTGAAA-3' (reverse primer), and 5'-ACTTAACAATGGATATTTGAT-3'(sequencing primer). The pyrosequencing assay was carried out via the protocol recommended by the manufacturer, with the use of PSQ96 (Pyrosequencing AB, Uppsala, Sweden).

RESULTS

Clinical features

Patients included in the study were 191 (33M; 160F; female 83%). The average weight was 124 kg, mean BMI of 46 kg/m^2 (36–66), 167 patients had morbid obesity and 24 severe obesity. The average excess weight loss at 18 months was 72% (SD ± 18%), the post-op mean BMI was 29 kg/m^2.

32% of patients (62pt) suffered from hypertension before surgery, postoperative 47% (29pt) experienced an improvement in hypertension with decreased amount of drugs taken, 48% (30pt) hypertension was cured with drug discontinuation (95% cure + improvement).

20% of patients (38pt) had diabetes type II before gastric by pass, after surgery 31%(12pt) improved by reducing the intake of insulin and oral antidiabetics, 64% healed and has discontinued medication (improvement + cure 95%).

Before surgery 55 patients (29%) had glycated hemoglobin value greater than 6.0%,18 months after surgey 37 patients (65%) had fallen below 6.0%.

MC4R mutational and SNP rs7566605 genotyping analyses

In *MC4R* gene, 5 distinct changes were found in 9 unrelated patients (4.6%). Of them, two changes, the substitutions V103I (rs2227916, c.307G>A) and I251L (rs52820871, c.751A>C) were previously reported as gain-of-function mutations in *MC4R* modulating the receptor activity and then responsible for a preventive obesity (voir mon resumé Hum Mol Genet. 2007 Aug 1;16(15):1837–44.). Two substitutions, p.Asp90Tyr (c.268G>T) and p.Asp298Asn (c.893G>A), are never reported so far and involved two conserved acidic amino acids lying within the third and seventh transmembrane regions, repectively. In absence of functional studies and using *silico* predictions (i.e., SIFT, PolyPhen V2), there is insufficient evidence to conclude novel variants as

possibly damaging or benign changes. However, a PolyPhen score higher than 2.9 is observed for the p.Asp90Tyr substitution suggesting deleterious consequences on melacortin 4 receptor. The last change, a frameshifting deletion (c.750_751del2, rs13447339) is considered as causative MC4R mutation (Table 1 Reprenant les données cliniques, la mut, les csq sur la proteines et les scores PolyPhen par ex). Additionally, were found 17 (8.7%) CC homozygotes for the rs7566605 single nucleotide polymorphism. Interestingly, no carriers of MC4R mutation were found to be homozygous for the rs7566605 SNP.

Correlations between molecular background and clinicopathological data

The global population affected by mutation was characterized as follow: female 85%, pre-op average weight 124 kg, pre-op mean BMI 45 kg/m^2 (38–54), morbid obesity 23 patients, severe obesity 3 patients.

The population affected by mutation of the gene INSIG2 was so marked: female 82%, pre-op average weight 124 kg, pre-op mean BMI 45 kg/m^2 (38–54), morbid obesity 16 patients, severe obesity 1 patient.

The population affected by mutation of the MC4R gene was characterized as follow: female 89%, pre-op average weight 125 kg, pre-op mean BMI 44 kg/m^2 (39–51), morbid obesity 7 patients, severe obesity 2 patients. Table 1 summarizes the various types of mutation of this gene.

The feeding behavior of the various groups is summarized in Table 2.

The curves of weight loss 18 months after surgery of patients with and without mutation is shown in Figure 1 and shows a no-significant difference in weight loss of different groups.

The analysis of the variation of postoperative comorbidities (hypertension and diabetes) is summarized in Tables 3,4 and Figure 2,3. Table 5 shows the postoperative change in glycated hemoglobin. Table 6 refers to the postoperative behavior of cholesterol and triglycerides. Table 7 summarizes the statistical values of p for excess weight and comorbidities.

All the tables take into account the population without mutation (M-), the global population with mutation (M+) and the patients with the two mutations of the genes INSIG2 and MC4R separately, except cholesterol and triglycerides that were compared only between M- and + due to the few patients.

DISCUSSION

In 2002, were published the results of a study comparing the cost of obesity surgery in England with the costs of comorbidity caused by obesity: surgical costs vary from 45.8 million pounds (52.1 million euros)and 49 million pounds, the cost of treating comorbidities of morbid obesity was around 1075 million pounds a year[11].

With regard to childhood obesity, according to the World Health Organization, 1 of 5 boys in Europe is overweight. Each year, with more than 14 million young Europeans are overweight, of which 3 million obese, are added every year 400 thousand new overweight. [12-15]. The data for 2010 are even more alarming. The rate of obesity and overweight is 38.2% of which 10% are obese [12]. In addition, recent data indicate that overweight children tend to remain obese as adults [13]. In Europe about 1 million deaths are attributable to obesity each year. The WHO has estimated that 6% of European health spending is attributable to adult obesity [15].

From a Swedish study published in the BMJ, where they analyzed the combined effects of smoking and overweight adolescents, it appears that mortality is the same in obese non-smokers and smokers of normal weight, more than twice than non-smokers of normal weight. Similar results for the overweight [16]. In essence, obesity kills as much as smoking. Lots of numbers emphasize the importance of a health problem that is affecting the entire world and that justifies the enormous resources that are being used to study the disease from different points of view. In this study we tried to take two, genetics and obesity surgery, to analyze how one interacts with the other.

The genetic mechanism of body weight regulation is complex, presumably involving a large number of genes. Gene variants that have a slight influence on body weight are called polygenes are common in the general population and are different from person to person. On the contrary, there are individual genes that are able alone to influence body weight [17]. This study examined how monogenic defect ie MC4R gene or susceptibility factor ie SNP rs7566605 in the vicinity of *INSIG2* may influence response to obesity surgery.

Currently more than 70 different MC4R mutations are known, most of them associated with individuals suffering from morbid obesity [3,18-21]. In literature the frequency of these mutations in obese population varies from 2% to 5%. In our study, the percentage was 4.6%. Individuals with this mutation have a significantly higher BMI of the healthy population, 4.5 kg/m2 and 9.5 kg/m2 in men and women respectively [22]. In *MC4R* gene, of 5 distinct changes found, two substitutions V103I and I251L were previously reported as current changes with allelic frequencies varying from 0.049 to 0.143 and 0.069 and 0.129, respectively (http://www.ncbi.nlm.nih.gov/SNP/). Despite evidence for

preventive action on the regulation of weight [23], we didn't observe among our cohort association between these two SNPs and a more efficient response to surgery (Table 2).

In details, even in the absence of a control group of normal-weight people, we observed similar mean BMI in patients carrying MC4R mutation (44 kg/m^2 +/-écart type), in comparison obese population negative for MC4R coding region sequencing (46 kg/m^2 ± écart type). Again, BMI of the patients homozygous CC did not differ from that of obese population homozygous GG or heterozygous GC (45 kg/m^2 ± écart type). First described in a cohort of 288 families (Framingham Heart Study), the SNP rs7566605 INSIG2 gene was associated, in the homozygous CC form with susceptibility to obesity adult and child population [10]. About 10% of the studied population were carriers of the CC genotype [10]. In our study, the percentage was lightly lower 8.7%. The association with obesity of this mutation was confirmed by three other studies, the risk of becoming obese increased by 30% in subjects carrying the homozygous CC genotype [10]. Subsequently other studies have not confirmed the association between the rs7566605 polymorphism and obesity [24-28] Other contradictory results for this gene was given by 2 studies of lifestyle interventions: adults with homozygous CC undergo significant weight loss and the same is not true for a study of 293 obese children who lose significantly less weight than the control group without the mutation [29-30]. A 2009 study assumed that this discrepancy may be due to homogeneity that results from different types of population, mixed or stratified, in addition to environmental influences as evidenced by the different results in different ethnic groups [31].

In our study homogeneity is given by obesity and surgery that are common to all patients, the heterogeneity is caused by the different ethnic groups of the population: Luxembourg, Portuguese and Italians.

As for the feeding behavior was not found a statistically significant difference between patients with and without mutation. In a 2003 study Branson concludes that carriers of mutations in the MC4R gene are 100% binge eating [32], this data was later disputed by other studies [33]. In the present study, carriers of this mutation with type of eating disorder binge eating were only 56%, a result that goes against Branson conclusion.

The weight loss curve shown in Chart 1 shows no statistically significant difference between groups, the group with the lowest EWL at 18 months consist of patients with mutations in the gene INSIG2 and, paradoxically, the one with the highest EWL are patients with mutation on MC4R gene.

If we look at the post-operative medical history of hypertension, diabetes and variation and the values of glycated hemoglobin, even in this case there were no statistically significant differences. Same result was obtained for cholesterol and

triglycerides. Only statistically significant value was the one that compares the population affected by mutation in the gene INSIG2 and the healthy population as regards the values of glycated hemoglobin (00.2). This value is given by the high percentage of patients with type II diabetes in the population with INSIG2 gene mutation, not found in the literature and perhaps caused by increased insulin resistance and by the very effectiveness of gastric bypass on this disease associated with obesity.

In literature there are only two earlier works that analyze genetic mutations that lead to obesity in a group of patients undergoing bariatric surgery. Both consider patients undergoing gastric banding. One investigates the rate of postoperative complications in patients with mutations in the MC4R gene and concluded that these patients are not associated with a higher rate of complications post-op. The other study examines some single nucleotide polymorphism associated with insulin resistance in obese patients undergoing LAGB and find statistically significant differences in weight loss between patients with and without mutation [34–35].

Our study is based on patients undergoing bariatric surgery with a restrictive and malabsorpitive procedure and not just restrictive as in the case of the two papers mentioned above. In our study there were no statistically significant differences between patient with and without mutation for weight loss and comorbidities associated to morbid obesity, except for the above mentioned value of glycated hemoglobin in mutation of INSIG2 gene already commented.

As already mentioned, patients with mutations in the MC4R gene are affected by hyperphagia. They are already underway studies on mice to find a molecule agonist of the receptor that would alleviate the hyperphagia. In June 2010 was published a study on various selective agonist of the MC4 receptor based on spiroindane amide; this study shows a significant reduction in energy intake and weight loss of mice [36].

Conclusion

The study allowed to determine and confirm the literature data about frequency mutations of the MC4R and INSIG2 gene in a population suffering from morbid obesity, and to examine the influence of these mutations on obesity related comorbidity and weight loss in patients undergoing laparoscopic GBP.

The simplicity of the method allows us to imagine an highly reproducible scenario for all the mutations that affect body weight.

Mutations in MC4R and INSIG2 gene do not affect weight loss in patients undergoing gastric bypass. The study confirms the high effectiveness of gastric bypass on comorbidities associated with morbid obesity, particularly diabetes type II.

This is the first genetic study that takes into account the gastric by-pass as surgical technique.

Our study together with literature review emphasize the enormous resources that are being used in the study of obesity to identify the genetic causes, already coming to practical solutions in the case of obesity caused by mutations in the MC4R gene with the synthesis of an effective agonist against hiperphagia and body weight and the importance of bariatric surgery that has a high efficacy in obese patients with or without mutations and is still the only effective long-term treatment.

Future

Correspondence between genetic variation and clinical response (dietary and psychological) of an attitude of hyperphagia, in which the mutation may be a marker for the secure identification of patients with a certain feeding behavior, may be in future a stimulus to analyze long-term results of this population separately.

The population of obese patients is not homogeneous: different feeding behavior, differences in appearance and timing of co-morbidities, the difference in response to technical restrictions, the long-term failures. Identification of patients who may experience a long-term failure are being researched to try to characterize the homogeneous groups from the point of view of genetic expressivenes that is a certain and unchangeable data.

The clinical relevance and the research of the therapeutic algorithm remains an interesting and challenging point for further research.

TABLE 1 – MC4R MUTATIONS

p.Val103Ile	5pt
p.Ile251Leu	1pt
Delezione GA (Leu250-TTG)(lle251-ATC)	1pt
p.Asp90Tyr	1pt
p.Asp298Asn	1pt

TABLE 2 – FOOD BEHAVIOR

	M-	**M+**	**INSIG2**	**MC4R**
Binge eater	40%	50%	47%	56%
Sweet eater	51%	62%	59%	67%
Volume eater	84%	81%	82%	78%
B+S+V	28%	31%	24%	44%

FIGURE 1 – EWL

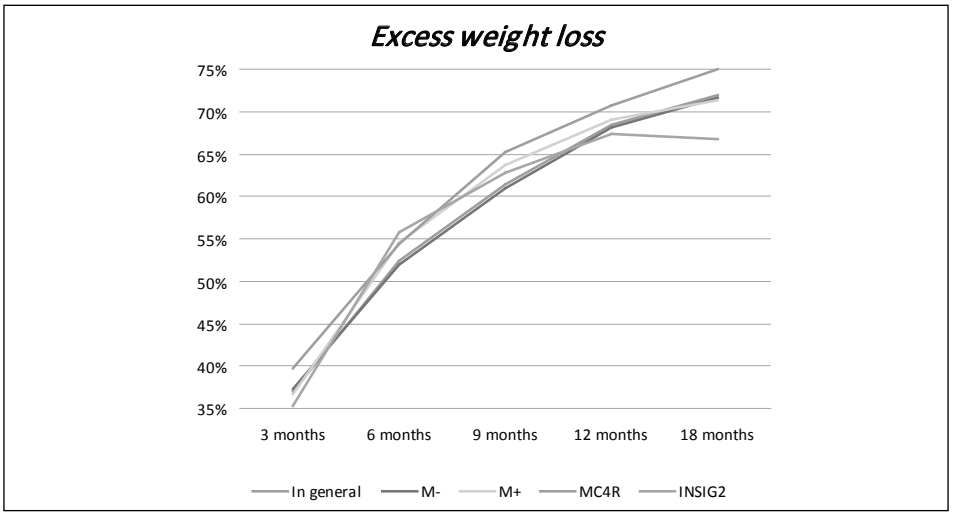

FIGURE 1 – EWL

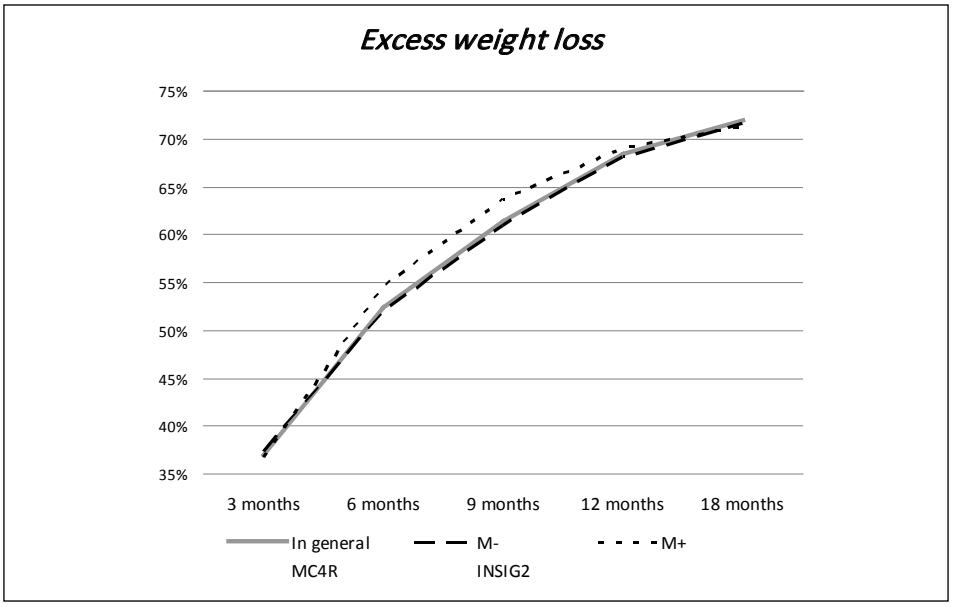

TABLE 3 – ARTERIAL HYPERTENSION

	M-	**M+**	**INSIG2**	**MC4R**
Pre-op	31%(50pz)	46%(12pz)	59%(10pz)	22%(2pz)
Miglio-ramento	44%(22)	58%(7)	50%(5)	100%(2)
Guarigione	50%(25)	42%(5)	50%(5)	0%
	M+G 94%	M+G 100%	M+G 100%	M+G 100%

TABLE 4 – DIABETES

	M-	**M+**	**INSIG2**	**MC4R**
Pre-op	19%(32pz)	27%(7pz)	35%(6pz)	11%(1)
Miglio-ramento	34%(11)	14%(1)	17%(1)	0%
Guarigione	64%(20)	71%(5)	67%(4)	100%(1)
	M+G 97%	M+G 86%	M+G 83%	M+G 100%

FIGURE 2 – Hypertension variations

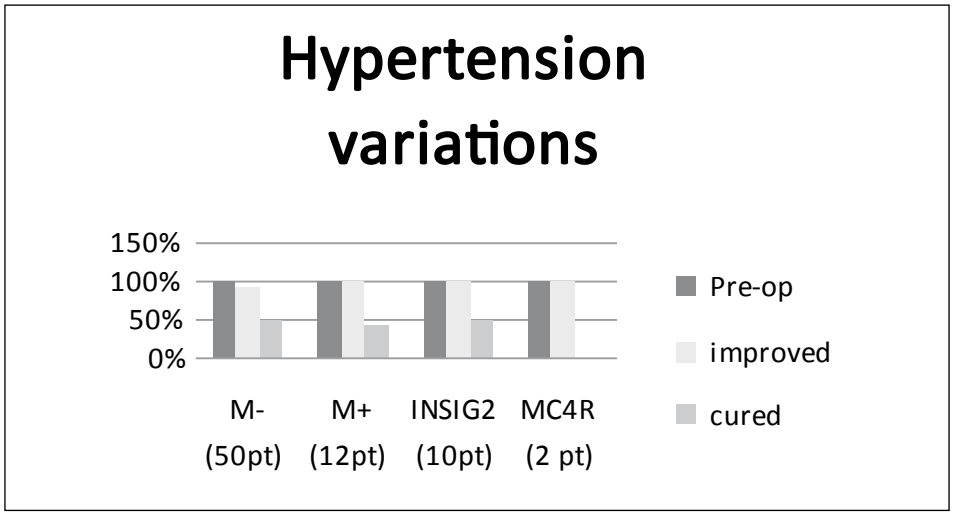

FIGURE 3 – Diabetes variations

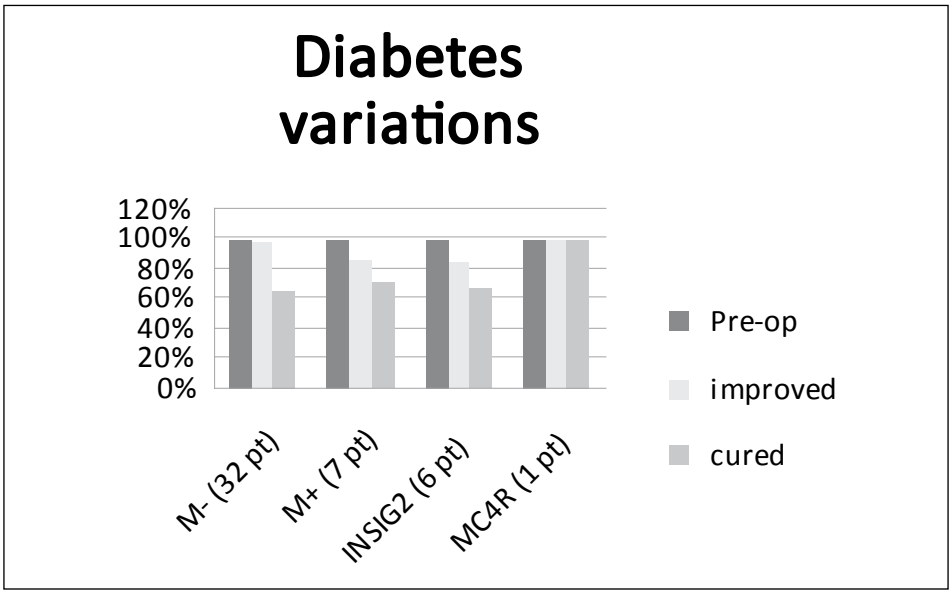

TABLE 5 – GLYCATED HEMOGLOBIN

	M-	**M+**	**INSIG2**	**MC4R**
Pre-op >6.0%	27%(45pz)	46%(12pz)	59%(10pz)	22%(2pz)
Post-op <6.0%	62%(28)	75%(9)	80%(8)	50%(1)

TABLE 6 – CHOLESTEROL-TRIGLYCERIDES

	M-	**M+**
Pre-op Col>220 mg/dl	24%	19%
Post-op Col<220 mg/dl	60%	40%
Pre-op Tgl>200 mg/dl	19%	23%
Post-op Tgl<200 mg/dl	81%	67%

TABLE 7 – STATISTICAL RESULTS

P VALUE

	M+	**MC4R**	**INSIG2**
EWL	0.37	0.64	0.14
Diabete	0.87	0.43	0.92
HbA1C	0.13	0.49	0.02
Ipertensione	0.18	0.43	0.07
Colesterolo	0.92	0.22	0.46
Trigliceridi	0.66	0.7	0.76

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Aktueller Stand und Perspektiven der Akutbehandlung des Schlaganfalls im Großherzogtum Luxemburg 2011

Actual state and prospects of acute stroke treatment in the Grand-Duchy of Luxemburg

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Abstract:

Stroke is a neurological emergency condition that warrants immediate hospitalisation on a stroke unit, where a dedicated team offers state-of-the-art diagnostic and therapeutic measures. Stroke units have shown to reduce mortality and handicap especially if thrombolysis is possible. A critical mass of stroke patients with standardised, simplified and automated processes is required to achieve good results. Stroke teams are no alternative to a stroke unit as a geographic unit. A turnover of less than 200–250 strokes per year is associated with a worse patient outcome and the treatment effect of a stroke unit may be abolished. The situation in Luxembourg offers the possibility to create units of this size and performance if all the concerned physicians and hospitals, health insurance and health administration join their efforts.

Key Words:

Stroke – Stroke Unit – Treatment

1. Einleitung

Beim Schlaganfall kommt es zu etwa 90% über einen Verschluss einer hirnversorgenden Arterie und in etwa 10% über eine Blutung ins Gehirn zu einer fokalen Funktionsstörung des Gehirns mit den Hauptsymptomen Lähmung, Sprachstörung, Gefühlsstörung und Sehstörung. Falls sich diese Ausfälle nicht zurückbilden kann es zu bleibender Behinderung, Verlust der Arbeitsfähigkeit und Hilfs-

bedürftigkeit (Pflege durch Angehörige, ambulante Pflege, Pflegeheim) kommen. Aus diesem Grund stellt der Schlaganfall einen erheblichen Kostenfaktor für die Kranken-, Pflege- und Pensionsversicherung, aber auch für die betroffenen Familien dar. Der Schlaganfall stellt nach Krebs und Herzinfarkt die dritthäufigste Todesursache in Luxemburg dar. Arteriosklerose und Herzerkrankungen sind die Hauptursachen des Schlaganfalls (1).

Neben der Prävention eines Schlaganfalls bei der Neurologen, Hausärzte und verschiedene internistische Disziplinen besonders gefragt sind, sind die effiziente Akutbehandlung und die Rehabilitation wichtig. In dieser Arbeit wollen wir die wissenschaftlichen Stand zur Lage der Akutbehandlung auf einer Stroke Unit allgemein und im Großherzogtum näher erörtern.

2. Die Stroke Unit

In der Akutphase kommt der Versorgung auf einer spezialisierten Einheit im Krankenhaus, einer sogenannten Stroke Unit (Schlaganfallspezialstation, Unité neurovasculaire) mit einer engen Verzahnung mit dem SAMU, der Notaufnahme und der Intensivstation des Krankenhauses sowie mit Rehabilitationskliniken eine besondere Bedeutung zu.

Eine solche Stroke Unit ist eine geographische Einheit, auf der fast ausnahmslos Schlaganfallpatienten und gefährdete Patienten behandelt werden. Auf einer Stroke Unit arbeitet ein speziell ausgebildetes und motiviertes Team von Neurologen, Pflegepersonal, Physiotherapeuten, Ergotherapeuten, Logopäden und Sozialarbeitern, das sich ständig fortbildet, um den Patienten eine Therapie nach dem jeweils neuesten Erkenntnistand anbieten zu können. Eine Stroke Unit arbeitet multidisziplinär mit den Kollegen aus der Neuroradiologie, der Kardiologie, der Neurochirurgie, der Anästhesie und der Gefäßchirurgie zusammen. Auf einer Stroke Unit wird zunächst rasch die Diagnose „Schlaganfall“ gestellt, ggf. wird ein verschlossenes Gefäß rasch rekanalisiert (Thrombolyse / mechanische Rekanalisation) (1). Die Stroke Unit ist die Organisationszentrale für die Akuttherapie und als ein Gesamt-Therapeutikum wie ein Medikament zu betrachten. Stroke Units reduzieren die Anzahl von Todesfällen und Behinderung um 18% (2). Im Falle einer Thrombolyse, die innerhalb von 4,5 Stunden nach Beginn der Symptome beginnen muss, ist der Nutzen weitaus höher. In einer Übersichtsarbeit, die 3670 randomisierte Patienten untersuchte, war ein günstiges Ergebnis (modified Rankin score 0–1) nach 3 Monaten 2,55 mal so häufig, wenn die Lyse innerhalb von 90 min begonnen wurde, 1,64 mal so häufig für einen Lysebeginn zwischen 91 und 180 min, 1,34 für einen Lysebeginn zwischen 181 und 270 min und 1,22 für einen Lysebeginn zwischen 271 und 360 min in der Lysegruppe im Vergleich zur nicht-lysierten Gruppe (3). Je höher also der Anteil lysierter Patienten ist, umso besser ist das Outcome.

3. Geographische Einheit

Zu Beginn unseres Jahrhunderts wurden oft „Stroke Teams“ propagiert. Dies ist eine kleine Gruppe mit mindestens einem Arzt und einer Schwester, aber auch mit Therapeuten, die sich auf den Schlaganfall spezialisiert hat und im Falle eines Schlaganfalls sofort verständigt wird und zur Stelle ist, um ihre Expertise mit den Behandelnden (z.B. Internisten, Anästhesisten und nicht auf den Schlaganfall spezialisierten Krankenschwestern) zu teilen. Eine randomisierte Londoner Studie ergab, dass Mortalität und Institutionalisierung der Patienten, die auf einer Stroke Unit behandelt worden waren geringer ausfielen, als bei Patienten, die durch ein Stroke Team behandelt worden waren (4). Eine systematische Review randomisierter Studien ergab keinen Unterschied bez. Tod und Abhängigkeit durch eine Stroke-Team-Behandlung im Vergleich zu einer Behandlung auf einer Allgemeinstation und einen deutlichen Vorteil durch die Behandlung auf einer Stroke Unit (5). Eine neuere ungarische Kohortenstudie mit 8743 konsekutiven Insultpatienten ergab eine Todesrate nach 28 Tagen von 12.6% in Stroke Units und von 15.2% in der Behandlung mittels Stroke Team (P = 0.002) (6). Langhorne et al diskutieren in Ihrer Metaanalyse eine Prozessoptimierung auf einer konsequent geführten Stroke Unit als Ursache des besseren Abschneidens (5). Wenn sich Therapeuten, Patienten und Angehörige häufiger sehen und wenn durch eine räumliche Nähe eine stärkere Observation des Patienten, seiner Krankenakte und seines Monitors stattfindet und wenn mit dem Schlaganfall vertraute Therapeuten involviert sind, stehen mehr Informationen zur Verfügung, es kommt zu weniger Übergabefehlern und die Therapie kann leitliniennah erfolgen. Darüberhinaus werden die Patienten und ihre Angehörige besser aufgeklärt und in den therapeutischen Prozess mit eingebunden.

4. Kritische Masse als Voraussetzung für Prozessoptimierung

Mehrere Studien konnten unzweifelhaft belegen, dass ein gewisser Umsatz auf einer Stroke Unit erforderlich ist, um eine hohe Qualität zu gewährleisten. Dies trifft für die Behandlung auf der Stroke Unit an sich als auch für die Schlüsselprozeduren Thrombolyse / mechanische Rekanalisation und Endarteriektomie der A. carotis zu. In einer kanadischen Übersicht wurden 26,676 Patienten mit ischämischem Schlaganfall untersucht, die in 606 verschiedenen Spitälern aufgenommen worden waren (7). Die Mortalität und die Häufigkeit von Komplikationen waren signifikant mit der Anzahl der behandelten Schlaganfallpatienten korreliert. Je mehr Schlaganfallpatienten behandelt wurden, umso weniger verstarben (vgl. Tabelle 1).

Anzahl der behandelten Schlaganfallpatienten pro Jahr	Mortalität nach 7 Tagen	Mortalität während des gesamten stationären Aufenthaltes
<50	9,5%	18,2%
100–199	7,3%	15,2%
≥200	6,0%	12,8%

Tabelle 1: Mortalität nach Schlaganfall in Abhängigkeit von der Anzahl behandelter Patienten pro Jahr und pro Zentrum (nach multivariabler Adjustierung) (7).

Weiterhin kam es zu weniger Pneumonien und Harnwegsinfekten in größeren Zentren (7).

Ähnliches wurde in den Niederlanden in einer nationalen Studie an 73,077 Schlaganfallpatienten von 2000 bis 2004 festgestellt. Patienten, die in einem Spital mit mehr als 200 Schlaganfallpatienten pro Jahr behandelt wurden, starben nach 7 Tagen weniger als halb so häufig (Odds Ratio 0,45, Konfidenzintervall 0,20–0,99 als Patienten, die in einem Spital mit weniger als 50 Schlaganfallpatienten pro Jahr behandelt wurden (8). *Das bedeutet, dass der Effekt einer Stroke Unit durch eine zu geringe Fallzahl aufgezehrt werden kann..*

Ein linearer Zusammenhang besteht zwischen der Überlebensrate während des stationären Aufenthaltes nach Thrombolyse und der Anzahl der Thrombolysen im betroffenen Zentrum: Pro zusätzlichem mit tPA behandeltem Patienten pro Jahr steigt die Überlebensrate um 3% (9). Konkret heißt das, dass in einem Zentrum mit 25 Thrombolysen pro Jahr die Mortalität um etwa 60% geringer ist als in einem Zentrum mit 5 Thrombolysen pro Jahr. Die Autoren postulieren, dass es in Zentren mit weniger Erfahrung möglicherweise häufiger zu Protokollverletzungen kommt.

Das Gleiche trifft für Endarteriektomien der A. carotis zu: Eine Studie aus dem Staat New York an 28 207 Patienten belegt den Einfluss eines hohen Umsatzes auf die Mortalität (vgl. Tabelle 2) (10).

Jährliche Operationszahl	Mortalität im Krankenhaus [%]
1–4	2,13
5–9	1,45
10–14	1,2
15–24	1,09
25–49	0,97
>49	1,01

Tabelle 2: Abhängigkeit der Mortalität von der jährlichen Karotisoperationszahl (10).

Kanadische Chirurgen mit geringem Umsatz in Spitälern mit geringem Umsatz haben ein 3,5-mal höheres Komplikationsrisiko als Chirurgen mit hohem Umsatz aus einem Spital mit hohem Umsatz. Die Autoren folgern „that surgeons with low case volumes should not be performing carotid endarterectomy“ (11).

Worin liegen die Gründe für ein besseres Abschneiden der Patienten, die in einem Zentrum mit einem hohen Umsatz behandelt werden? Zum einen ist es ganz banal die größere Erfahrung des einzelnen Therapeuten, die zu besseren Ergebnissen führt. Der Schlaganfall stellt im Gegensatz zum Herzinfarkt eine komplexe multikausale Erkrankung dar die ein sehr differenziertes Vorgehen, angepasst an die Insultätiologie, erfordert. Dieses differenzierte Vorgehen auf neuestem Stand kann nur in einem multidisziplinären Team mit häufigen Besprechungen und häufigem Sich-in-Frage-Stellen sowie dauernder spezialisierter Fortbildung erreicht werden. Solche Besprechungen mit Informationsaustausch finden häufiger in größeren Einheiten statt (12), weil es sich schlicht und einfach nicht lohnt, für eine geringe Zahl von Patienten solche interdisziplinären Konferenzen abzuhalten und bei einem kleinen Therapeutenteam immer einige fehlen. Das Arbeiten in einer therapeutischen Gruppe mit einem Ziel ist hierbei einem „Einzelkämpfermodell“ deutlich überlegen. Hierbei ist eine „kritische Masse“ erforderlich. Die moderne Medizin ist zu komplex geworden und ändert sich zu schnell, als dass jeder Arzt jede Krankheit auf hohem Niveau behandeln kann. Leider ist diese Auffassung aber in der historisch bedingt dezentral tätigen luxemburgischen Ärzteschaft weit verbreitet. Es wäre im Sinne des Patienten wünschenswert, Kompetenzzentren zu schaffen, was erfreulicherweise z.Zt. geplant ist. Zum anderen gibt es in der Behandlung des Schlaganfalls auch ein stereotypes Vorgehen, das sich gut operationalisieren lässt. Hierbei spielen Prozesse wie Vereinfachung, Standardisierung und Automatisierung die entscheidende Rolle (13). Solche Prozesse sind z.B. rasche Diagnose, rasche Bildgebung (door-to-CT time), rasche Thrombolyse (door-to-needle time) bzw. mechanische Rekanalisation, rasche Ursachendiagnostik, Frühmobilisation und Sekundärprävention mit festen Protokollen (14). Hierfür ist ein gut eingespieltes Team ohne hohe personelle Fluktuation erforderlich, das diese Schemata kennt und konsequent anwendet. Kleine Einheiten bein-

halten zwangsläufig eine geringere personelle Verzahnung und Konstanz, z.B. im Krankheitsfall oder während der Erholung nach einem Dienst. Wenn eine Stroke Unit z.B. nur über eine Krankengymnastin verfügt und diese krank wird, kommt eine Vertretung, die sich aber evtl. vor allem mit orthopädischen Patienten gut auskennt. Wenn 2 Krankengymnastinnen zuständig sind, ist eine Konstanz gewährleistet und die Vertretung kann ggf. nachfragen und sich abstimmen. Deshalb sind größere Einheiten auch hier von Vorteil.

Diese Überlegungen haben sich in den aktuellen Empfehlungen der Deutschen Schlaganfallgesellschaft widergeschlagen. Für eine regionale Stroke Unit wird ein Durchsatz von mindestens 250 Schlaganfällen/TIAs pro Jahr gefordert und für eine überregionale 450. Darüber hinaus besteht eine Mindestanforderung der Thrombolysehäufigkeit: Es müssen mindestens 16 Patienten pro Jahr lysiert werden (15).

5. Aktuelle Lage im Großherzogtum

Nach den Empfehlungen der „Société Luxembourgeoise de Neurologie“ gibt es 3 Stroke Units im Großherzogtum, eine in Ettelbrück (3 Betten, in die Intensivstation integriert), eine in Esch/Alzette (4 Betten, in die kardiologische Intensivstation integriert) und eine supraregionale am CHL in der Stadt (6 Betten, in die Neurologie integriert) (16). Diese Stroke Units nehmen an einem Benchmarking mit insgesamt 135 Kliniken aus Deutschland und der Schweiz teil. Am CHL wurden 2010 220 dokumentierte Patienten mit Schlaganfall/TIA behandelt (17). Davon wurden 14 lysiert. In großen Zentren werden über 20% lysiert (18). Hieraus wird ersichtlich, dass eine weitere Zersplitterung der Stroke-Unit-Landschaft in der Stadt Luxemburg unbedingt vermieden werden muss, um eine hohe Fallzahl und eine hohe Qualität der Schlaganfallversorgung sicherzustellen. Dem entgegen steht das historisch gewachsene aber unglückliche System der Dienstrotation in der Region Centre, nachdem das CHL und der Kirchberg jeweils 40% der Zeit und die Klinik Sainte Thérèse 20% der Zeit Dienst haben und theoretischerweise während dieser Zeit alle Schlaganfälle aufnehmen. Diesem Dienstsystem ist das Personal in den verschiedenen Kliniken angepasst (Neurologen, Radiologen, Techniker für das MRT, andere Ärzte, Pfleger, Therapeuten). Keine Klinik könnte ohne personelle und strukturelle Aufstockung bzw. personelle Zusammenarbeit mit Personal von außen alle Patienten mit Schlaganfall 24/24 Stunden versorgen. Nur durch eine zentralisierte und transparente Zusammenarbeit in der Region Centre lässt sich eine kritische Masse der Schlaganfall-Versorgung erreichen. Die Société Luxembourgeoise de Neurologie hat schon 2002 ein solches Konzept unterstützt (16). Schwierigkeiten sind z.B., dass eine strikte Trennung von allgemeinneurologischem Dienst und Stroke-Unit-Dienst nur für die Patienten möglich ist, die vom Notarzt gebracht werden und wo der SAMU sicher die Diagnose Schlaganfall gestellt hat und dass die Arbeit an verschiedenen Spitälern für einen Arzt sicher nicht einfach ist. Da die meisten Schlaganfälle am Tag auftre-

ten, wäre als pragmatische Zwischenlösung eine Aufnahme der Schlaganfälle auf der zentralen Stroke Unit während der Dienstzeit (z.B. 8:00–18:00) von Montag bis Freitag und zu den Zeiten, wo dieses Krankenhaus sowieso Dienst hat. Dies würde dazu führen, dass etwa 72% aller Patienten mit Schlaganfall aus der Region Centre auf der Stroke Unit am CHL behandelt werden könnten (eigene Berechnungen anhand der Zahlen aus dem CHL) mit einer geringen Personalaufstockung und ohne dass Ärzte aus anderen Spitälern am CHL arbeiten müssten. Dieses Vorgehen ist ethisch sicher nicht perfekt, weil dann nicht alle Patienten Zugang zur zentralisierten Stroke Unit haben, aber eine Annäherung an die international üblichen strukturellen Gegebenheiten. In einem zweiten Schritt könnte dann eine gemeinsamer neurologischer Dienst aufgebaut werden. Eine transparente Erfassung des Daten des Notdienstes (z.B. wie oft wird die Nummer 112 wegen eines Schlaganfalls angerufen und wird der Patient in die entsprechende Pflegekette eingebunden?) muss damit einhergehen.

6. „Comprehensive Stroke Units“

Die Zukunft gehört den sogenannten „Comprehensive Stroke Units“, d.h. einer Stroke Unit, auf der nicht nur die Akutversorgung erfolgt, sondern auch die Weiterversorgung bis zur Verlegung in eine Rehabilitationsklinik (oder nachhause bzw. in ein Heim). Häufig wurde der Patient zunächst noch auf eine neurologische Allgemeinstation verlegt. Dies führt oft zu einer Unterbrechung der ärztlichen, pflegerischen und und therapeutischen Kontinuität. Konkret bedeutet dies, dass direkt neben der Stroke Unit noch Betten sind, die vom selben Team betreut werden, wie die akute Stroke Unit. Eine finnische Beobachtungsstudie an 61 685 Patienten hatte ergeben, dass die Number-needed-to-treat um einen Todesfall oder eine Institutionalisierung nach einem Jahr zu verhindern bei 29 für die Comprehensive Stroke Units und 40 für akute Stroke Units lag im Vergleich zu Allgemeinstationen (19). Die Vorgehensweise am CHL versucht, diesem Modell Rechnung zu tragen.

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7-Year Results of Cell Therapy in Patients with Severe Ischemic Cardiomyopathy

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Abstract

Background: Intracoronary infusion of autologous bone marrow cells (CTX) has been shown to improve myocardial function in post infarct patients and in patients with chronic ischemic cardiomyopathy. Long term results of CTX are unknown.

Methods and Results: In this small pilot study, eleven patients with chronic ischemic cardiomyopathy and ejection fraction (EF) of 19±1% were treated with CTX and followed for 7 years. Four patients died during follow-up, all because of progressive heart failure. All patients received an implantable cardioverter defibrillator (ICD) during the course of the study but only 1 patients developed ventricular tachycardia after CTX. One patient received resynchronization therapy. The overall clinical benefit of CTX was modest (NYHA 3.0±0.1 pre and 2.5±0.2 post CTX, p= 0.06). CTX was not associated with reverse remodeling. However, left ventricular EF (19±1% pre and 18±6% post) and left ventricular end-diastolic volumes (289±71 ml pre and 294±123 ml post) remained remarkably stable over 7-year follow-up in the survivors of this very sick population.

Conclusions: During 7-year follow-up, CTX was associated with stabilization of EF and ventricular volumes but without significant clinical benefit or evidence of reverse remodeling.

Key words: heart failure – cell therapy – ischemic cardiomyopathy

Introduction

Despite adequate reperfusion, chronically ischemic (hibernating) myocardium may persist after myocardial infarction in association with variable degrees of scar tissue. This is associated with left ventricular (LV) remodeling and chronic heart failure in many patients. Ten years ago, the first reports demonstrating possible myocardial regeneration in animals after infusion of bone-marrow derived cells (CTX) were soon followed by a wave of clinical trials. Although the results of the trials were not unequivocal, four meta-analyses of CTX in the setting of acute MI have demonstrated the feasibility and safety of this approach and also a modest benefit on left ventricular ejection fraction (EF) with an increase of 3% (1–4).

While this modest improvement in cardiac function may be trivial in patients with preserved EF, this may not be the case in patients with severe LV dysfunction. Indeed, a post hoc analysis of the REPAIR-MI trial has indicated that CTX is most effective in patients with markedly depressed LV function (5). Along the same line, Strauer et al. recently reported the findings of intracoronary CTX in 191 patients with heart failure (STAR-heart study) (6). This open label and non-randomized trial reported a significant increase in EF between baseline (29%) and follow-up at 3 months (36%) with a plateau between 3 months and 5 years.

The long term effects of CTX in patients with markedly depressed LV function are unknown. We have studied the effects of intracoronary CTX in patients with markedly depressed EF (19%) in a small pilot trial. The short term results have been published elsewhere (7). The current study was focused on 7 year results.

Methods

Patient population and evaluation

The present study consisted of 11 patients with end-stage ischemic cardiomyopathy who had an EF of 19±1% by single-photon emission computed tomography (SPECT) gated imaging, were in NYHA functional class 3 despite maximal medical therapy and who were not a candidate for myocardial revascularization or heart transplantation. This was a prospective, nonrandomized, open-label single center study. The study was approved by the local Ethics Review Board. All patients

signed an informed consent. The subjects were enrolled between April 1, 2004 and October 15, 2004.

Baseline evaluation included a complete clinical evaluation, a complete laboratory evaluation including determination of pro-brain natriuretic peptide (BNP), stress exercise SPECT imaging, gated imaging, stress exercise echocardiography, and 24-hour Holter monitoring. A complete echocardiogram was performed at 24 hours, after one week, after one month and yearly thereafter. Gated SPECT imaging was also repeated at 4 months and after 7 years. The investigators performing echocardiography and nuclear testing were blinded to clinical and laboratory data.

Bone marrow aspiration and isolation of mononuclear cells

Bone marrow aspiration was performed in aseptic conditions using standard clinical procedure guidelines. Fifty ml of bone marrow were obtained through 10 consecutive iliac crest punctures via the same access after local anesthesia and conscious sedation with i.v. midazolam. Mononuclear cells were isolated as previously described (7) and resuspended in X-VIVO 10 culture medium (Bio Whittaker, Belgium) supplemented with 20% of autologous serum (final volume = 10 ml).

Intracoronary delivery of mononuclear cells

Bone marrow aspirates were obtained in the morning of the day of the cell transplantation in the catheterization laboratory. All patients received aspirin, clopidogrel, heparin and a bolus of abciximab. Cells were infused through an over-the-wire balloon advanced into the proximal part of the infarct artery as previously described (7).

Imaging studies

Echocardiography was performed on a phased array GE Vivid 7 imaging device equipped with a 1.5-4.0-MHz transducer as described previously (7). All echocardiographic and Doppler data were stored digitally at baseline and at the end of each workload step for further off-line analysis. For each measurement, three cardiac cycles were averaged. Two-dimensional echocardiogams were acquired in parasternal short-axis view, apical long-axis, four- and two-chamber views. The area-length method was used to calculate ejection fraction.

To determine the interobserver variability, measurements were repeated by a second independent observer in 10 randomly selected patients. The variability was measured by the correlation coefficients between the two measurements. Gated SPECT imaging was performed as previously described (7). All patients had a

history of myocardial infarction with a fixed defect and no reversible ischemia documented by SPECT imaging.

Statistical analysis

Comparisons were made with repeated-measures ANOVA and Wilcoxon signed rank test as indicated. A $p<0.05$ was considered statistically significant.

Results

Clinical findings

Patient population demographics are shown in table .1. All patients were on β-blockers, ACE inhibitors and diuretics. Two patients had an implantable defibrillator before enrollment. No patient developed a complication secondary to the procedure.

During 7-year follow-up, all patients received an implantable defibrillator because of new clinical trial results (MADIT 2) and guidelines. Only 1 patient developed non-sustained ventricular tachycardia. Biventricular pacing was implemented in 1 patient for LBBB. Four patients died during follow-up, all of them because of progressive heart failure. One patient died after 6 months, one patient after 12 months and two patients after 24 months. Three patients developed a stroke. There were several hospitalizations for decompensated heart failure but the majority of hospitalizations were related to implantations of a defibrillator. One patient underwent repeat cardiac catheterization to exclude stent thrombosis in the setting of chest pain and a very large collateral vessel was observed between infarct and contra-lateral artery.

The overall benefit of cell therapy was limited with a trend towards clinical improvement. Of the 7 survivors, 3 patients improved by one NYHA class or more. The levels of pro-BNP were not affected by CTX.

Echocardiography

Echocardiography findings over the 7-year follow-up are shown in table 2. The interobserver variability was low ($r=0.78$, $p=0.001$). The EF did not increase over the course of the study. At the same time, there was no change of enddiastolic and endsystolic dimensions.

Gated SPECT imaging

Gated SPECT imaging findings over the 7-year follow-up are shown in table 2. The EF did not increase significantly during follow-up. Left ventricular volumes remained stable during follow-up- Functional capacity of most patients remained

unaffected. On the other hand, in the survivors, no significant deterioration was noted in this sick population. Figure 1 shows nuclear images for a typical patient pre-CTX and after 7 years. Perfusion and volumes are unchanged. This was the case for all the patients.

Discussion

The present study describes for the first time the long term evaluation of CTX in patients with very severe end-stage ischemic cardiomyopathy and ejection fraction around 20%. The results of our study suggest that this approach is safe but not effective.

Our initial observation in the same cohort 4 months after CTX had indicated that exercise-induced cardiac strain and exercise-induced mitral regurgitation may improve after CTX (7). The current report demonstrates that this effect does not translate into significant long term clinical benefit.

The study by Perin et al. (8) demonstrated enhancement of regional and global LV function after intramyocardial injections of bone marrow-derived cells in 14 patients with severe heart failure (EF 30%). In the STAR-heart study including 191 patients with intracoronary cell delivery, EF also improved in the months following CTX (36 vs. 29%) and remained stable at 5 years (37%) (6).

Our findings are in contrast with those studies. Indeed, in our patient population, EF measured with echocardiography and gated SPECT imaging remained unaffected by CTX at 4 months and after 7 years. Left ventricular volumes assessed by the same techniques also remained remarkably stable. Of note, the studies by Perin et al. and by Strauer et al. included more patients with moderate LV dysfunction. In addition, in the STAR-heart study, EF was determined with quantitative ventriculography which is less accurate than echocardiography or SPECT imaging.

The most important finding of our pilot study is that CTX doesn't appear to induce measurable reverse remodeling in very severe ischemic cardiomyopathy. Our patient population was comparable to patients included in the Multicenter Automatic Defibrillator Implantation Trials (MADIT). For patients receiving an ICD in those trials, life expectancy has been calculated to be around 8 years (9). Our patient cohort compares favorably with those results. Whether this is due to stabilization of ventricular geometry and function by CTX can only be speculated. However, our study is limited by its small size and the lack of a control population.

We conclude that further pre-clinical work needs to be done before larger clinical trials of CTX are performed in patients with end-stage ischemic cardiomyopathy.

Acknowledgements

The authors thank Prof. Zeiher, for his help and collaboration. The authors also thank Malou Gloesener, Loredana Jacobs, Agnès Debugne and François Robert for expert research assistance.

Table 1. Demographics of the patient group at the time of CTX

Age (years)	64±2
Male gender (%)	91
Hypertension (%)	82
Diabetes (%)	27
Hypercholesterolemia (%)	82
History of smoking (%)	54
Previous myocardial infarction (%)	100
Previous percutaneous coronary intervention (%)	91
Previous coronary artery bypass grafting (%)	0
Previous stroke (%)	0
Peripheral artery disease (%)	9
Chronic renal failure (%) (creatinine > 1.5 g/dl)	36
Chronic anemia (%) (hemoglobin < 14 g/dl)	55
Multivessel disease (%)	64

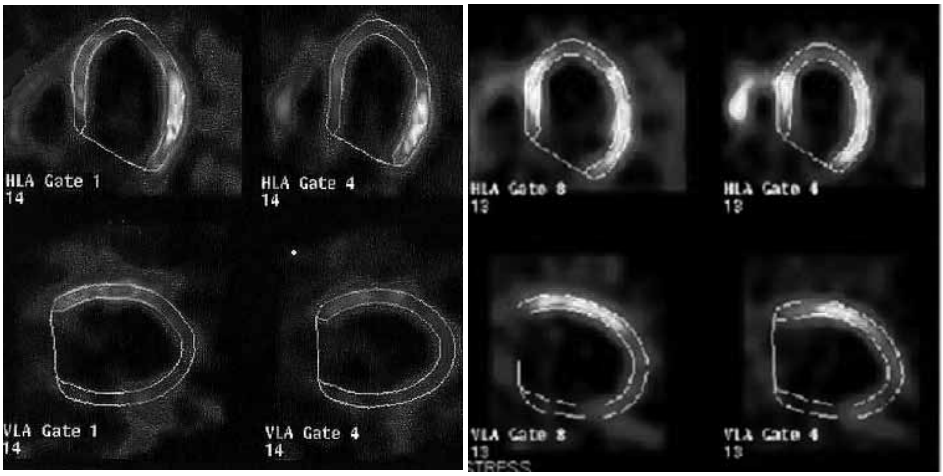
Table 2. Clinical characteristics and laboratory findings

	Baseline	**4 months**	**7 years**	**p**
NYHA	3.0±0.1	2.7±0.2	2.5±0.2	0.06
Systolic BP (mmHg)	113±6	116±5	121±5	NS
Heart rate (/min)	71±5	75±4	79±5	NS
EF (%, SPECT)	19±1	19±2	18±6	NS
EDV (ml, SPECT)	289±71	306±57	294±123	NS
EDD (mm)	67±2	69±3	65±9	NS
ESD (mm)	56±5	55±7	56±11	NS
Pro-BNP (ng/L)	4280±1477	5555±2356	5150±1999	NS

Functional capacity	72±24	77±32	65±26	NS
(W)				

NYHA, New York Heart Association functional class, BP, blood pressure, EF, ejection fraction, SPECT, single-photon emission computed tomography, EDV, end-diastolic volume, EDD, end-diastolic diameter, ESD, end-systolic diameter, BNP, brain natriuretic peptide, W, Watt

Figure 1



Gated SPECT imaging before (top) and 7 years after CTX (bottom).

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Lung Cancer Statistics in Luxembourg from 1981 to 2008.

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Abstract

Lung cancer is the leading cause of cancer-related death in the world and in Luxembourg. As a part of "*The health science initiative focused on personalized medicine*", Luxembourg aims to participate by developing diagnostics to improve the detection and treatment of lung cancer. In line with this objective, this study made a review of evolution of lung cancer in Luxembourg from 1981 to 2008 and compared this statistics to the situation in the Nordic countries, Europe in general and the World. Incidence data of the national *morphological tumour registry* and mortality data of the service of statistics of the *national ministry of health* is depicted in charts with trend lines, in the framework of a statistical evaluation of relevant parameters. The data indicate that while male lung cancer incidence decreased in Luxembourg, the incidence in women and its mortality have doubled over the 28-year span considered. Notwithstanding this increase, the female lung cancer incidence and mortality remain low compared to the Nordic countries and Europe. Interestingly, the study also potentially suggests that the lung cancer pattern follows the smoking pattern in incidence and mortality.

Key words: **Lung cancer, Luxembourg, Smoking**

1. Introduction

Lung cancer is the seventh most common cause of death in the world in 2011. It stands directly behind HIV/AIDS, which ranks sixth. Each year, 4 million people die of lung cancer, which represents 2.4% of the total number of deaths in the world each year (1). Lung cancer is also the leading cause of cancer-related death in the world (1, 2). This is particularly striking, considering that about 150 years ago, the disease was extremely rare or perhaps not diagnosed (3).

Data about lung cancer incidence and mortality in Luxembourg is published each year. Such data shows that lung cancer is the cancer most people die of in Luxembourg. A massive research agenda on lung cancer has been proposed in Luxembourg as a part of the "*personalized medicine*" initiative. CRP-Sante participates in this revolutionary concept with USA, and collaboratively they will put effort to generate a new idea for improving health and healthcare system. The result of this effort has been targeted to three primary facets of medicine: first more accurate and early assessments of disease risk; second better predictions of responses to treatment; and third safer, more effective treatments. In a nutshell, the initiative aims not only to provide tailor-made medicine but also to reduce medical cost in the ever growing health care sector.

As a key player in this program, scientists in Luxembourg research platforms will be involved in developing test(s) to improve the detection and treatment of lung cancer. A pivotal necessity of such a targeted disease research objective is a statistical analysis of the evolution of that particular disease in the local population. This is critical because most research material, which includes blood and tissue sample will be obtained from local clinics and hospitals and therefore the research study would be primarily conducted on local population. Also the research findings will have to be initially implemented to the local population before putting it through worldwide. In regard to this, this study has been conducted to analyze trends in the evolution of lung cancer in Luxembourg from 1981 to 2008 and evaluate significant statistical parameters to assess the situation of lung cancer in the country and compare it to the situation in the Nordic countries, Europe and also worldwide. Another objective of this report was to bring lung cancer statistics and smoking statistics together and emphasise the link between smoking and lung cancer. According to Cancer Research UK, smoking accounts for almost 90% of all lung cancer cases, i.e. more than 1 million lung cancer deaths are essentially related to smoking.

2. Methods

The main part of this study is a chart-based review of the evolution of lung cancer in the Luxembourgish population from 1 January 1981 to 31 December 2008. Incidence data was taken from the *morphologic tumour registry* (MTR) in the Grand-Duchy of Luxembourg. The MTR collects about 95 % of all cancer cases diagnosed at the *national laboratory of health* (LNS) and publishes them each year (4, 5, and 6). A total of 4,470 new incidences of lung cancer were recorded by the MTR from 1 January 1981 to 31 December 2008. Mortality data was taken from the service of statistics of the National Ministry of Health which publishes the causes of death in Luxembourg every year (2). Over the 28-year span, 5,649 deaths were caused by lung cancer. The incidence and mortality data is combined with the demographic data of 1 January of the following year, e.g. for 1981: inci-

dence data from 1 January to 31 December 1981 is combined with demographic data from 1 January 1982.

Demographic data for the population of Luxembourg is taken from the *national institute of statistics and economic studies* (STATEC) (7). The Luxembourgish population is relatively small and has been growing from 365,600 inhabitants on 1 January 1982 to 493,500 inhabitants on 1 January 2009 (7). Hence, trend lines are used to identify key features, rather than solely relying on year-to-year comparison, which contains temporal fluctuations arising from the rather small size of the sample population. The 28-year-period averages and standard deviations are also calculated.

Large tables of raw data are omitted for the sake of clarity. Incidence and mortality data is presented in a three-fold form of effective, age-standardised and age-specific data. The effective data, i.e. the evolution of the absolute number of lung cancer incidence or mortality, gives a clear image of how the situation of lung cancer in Luxembourg has changed from 1981 to 2008. The age-standardised rate based on a world population, i.e. ASR (W), was chosen for this study, because it is the most commonly used standard population (8). For the age-specific data, the ages 0-24 and 80+ are merged into single groups respectively, whereas the ages 25-79 are subdivided into 5-year groups. This results in a total of 13 age categories, which are accompanied by cumulative frequency plots. The study also looks at the evolution of male-to-female ratios in incidence and mortality.

3. Results

Effective cases in Luxembourg

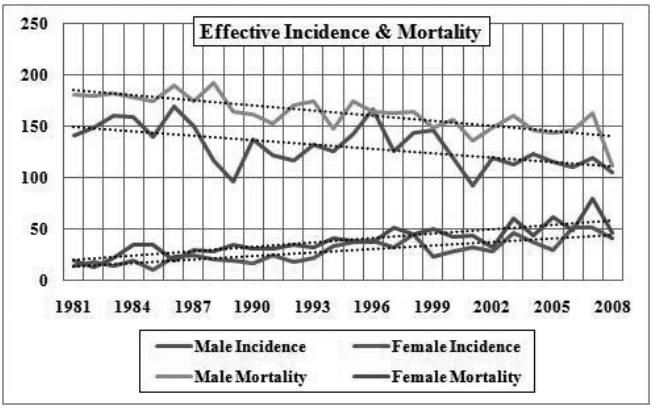

Figure 1: *Effective Lung Cancer Incidence and Mortality in Luxembourg (1981– 2008)*

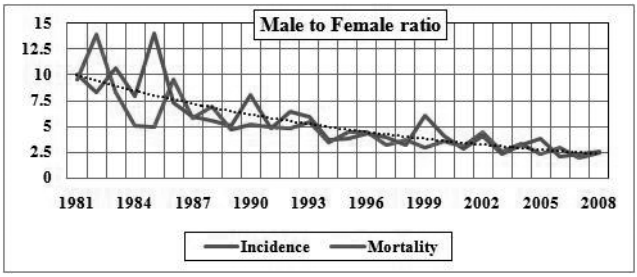

Figure 2: *Effective Male to Female Ratios for Incidence and Mortality*

From 1981 to 2008, 4,470 cases of incidence of lung cancer were recorded of which 3661 were male (81.9%) and 809 female (18.1%). The average of new incidences in Luxembourg is 160 with a standard deviation of 20. That is, on average 1 in 2500 or 0.04% of the Luxembourgish population are diagnosed with lung cancer each year in Luxembourg. The maximum number of incidences in a year for both genders combined was 206 cases in 1996 and the minimum was 116 cases in 1989. Male incidences fall in the range of 93 to 169 and female incidences lie between 10 and 52 cases respectively. (Figure 1)

Of the 5,649 cases of mortality recorded, 4,557 were male (80.7%) and 1092 female (19.3%). The average value for mortality is 202 with a standard deviation of 16. The maximum value for mortality combined was 243 cases in 2007, whereas the minimum occurred in 2008 and consisted of 158 cases. The male range goes from 112 up to 193 cases, whereas the female range varies from 13 to 80 cases. (Figure 2)

Effective male incidence and mortality are observed to be considerably higher than female incidence and mortality throughout the 28-year-period. One possible explanation elaborated further in the discussion is that incidence cases diagnosed in foreign countries are not reflected in the data from the Morphological Tumour Registry. However, effective male incidence and mortality are decreasing, while effective female incidence and mortality are increasing. As a consequence, the male-to-female ratio of new incidences and mortality, as shown in Figure 2, has come down from 10 :1 in 1981 to 2.5 : 1 in 2008.

Age-standardised rates

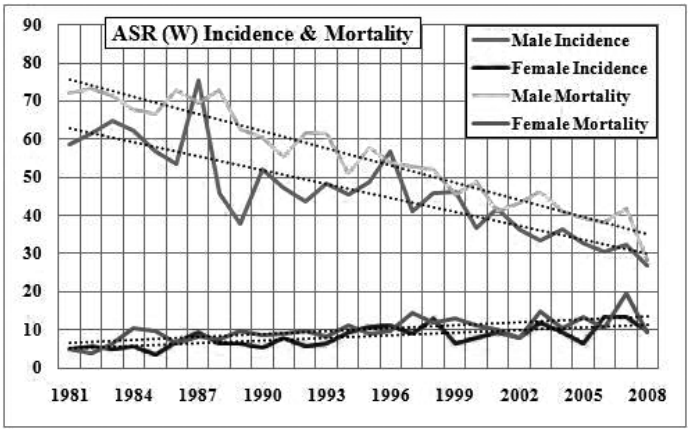

Figure 3: *Age-standardised rates (World) over time: Incidence*

The male ASR (World) for incidence has more than halved between 1981 and 2008: from over 60 incidences per 100,000 in the 1980s, down to under 30 incidences per 100,000 in the 2000s (Figure 3). The estimated annual change in male lung cancer incidence is –2.6%. The female ASR (W) for incidence, on the contrary, has doubled over the 28-year span, i.e. from about 5 incidences per 100,000 in the 1980s, to over 10 incidences per 100,000 in the 2000s. The estimated annual change in female lung cancer incidence is +2.5%.

The male ASR (W) for mortality has come down from above 70 to around 40 in recent years, which yields an estimated annual change of –2.1%. The female ASR (W) for mortality has tripled, i.e. increased from 5 cases per 100,000 in the early 1980s to 15 in the late 2000s. The approximate annual increase is estimated to be +3.9%.

Age-Specific rates

Figure 4: *Age-Specific Rates per 100,000 for Incidence & Mortality (1981–2008)*

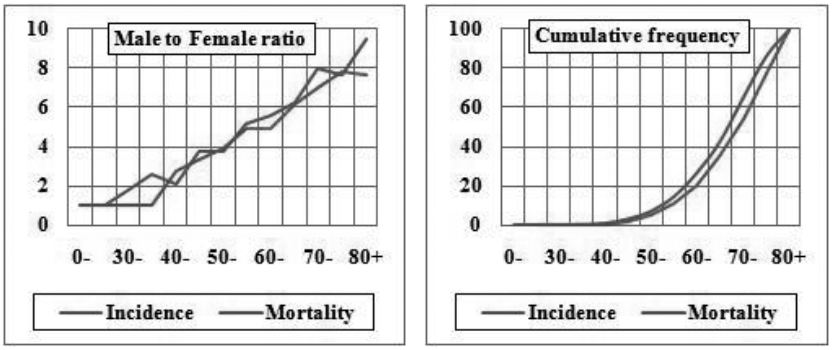

Figure 5: *Age-Specific Male to Female ratio & Cumulative frequency plots (in %) for Incidence and Mortality*

99% of all lung cancer incidences occur after the age of 40 and actually more than 80% after the age of 60 only (Figure 5). In fact, 86% of all male lung cancer incidences are confined in the range of 50 to 79, compared to 81% for females. The median of lung cancer incidence lies at 66 years for both genders. The highest age-specific incidence is observed in the 70 – 74 age group (Figure 4). 95% of all mortalities occur after the age of 50. The median of lung cancer mortality lies at 68 years for both genders. The highest age-specific mortality is observed in the 75 – 79 age group.

The male-to-female ratio for incidence and mortality increases with age (Figure 5). The increase is slightly sharper for incidence, where it is 1:1 up to the age group of 30–34 and increases linearly up to 9:1 for the 80+ age group. For mortality, the ratio starts to increase linearly from 1:1 for the 35-39 age group up to 8:1 for the 80+ age group.

To be able to compare male and female age group distributions adequately, we look at age-specific percentage distributions.

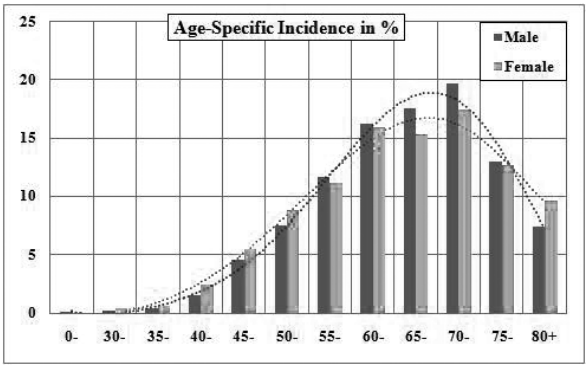

Figure 6: *Age-Specific Rates for Incidence in % (1981–2008)*

Incidence distributions are very similar for males and females (Figure 6). The peak is more significant in males (55–79 years), whereas the curve of females has marginally larger tails (on both sides) than the curve of males (under the age of 55 and over 80).

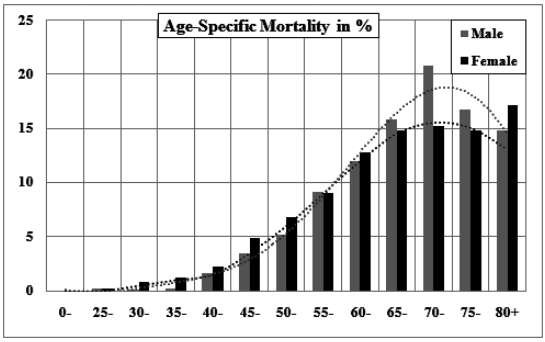

Figure 7: *Age-Specific Rates for Mortality in % (1981–2008)*

For age-specific mortality rates (Figure 7) we see that both distributions have peaks in the age group 70–74. The peak is higher in males than in females. The high value at 80+ for the female population arises from the fact that there is no distinction made among the age groups above 80, which explains the unusual high percentage in the female 80+ age group.

Most Common Cancers in Luxembourg – Incidence

From 1981 to 1987 (and probably before that), lung cancer was by far the most diagnosed cancer in the Luxembourgish male population (Figure 8). 25% of all cancers detected in males were lung cancers. Throughout the 28-year period, this percentage dropped and in 2008, lung cancer is only the 4th most frequently diagnosed cancer, now accounting for 10% of all cancers, behind prostate cancer, colon cancer and skin cancer. In the 1990s, prostate cancer became the most common cancer. Colon cancer remained stable, making up 10–15% of all cancers. Nowadays, stomach cancer goes down and skin cancer goes up and constitutes more than 10% of all cancers.

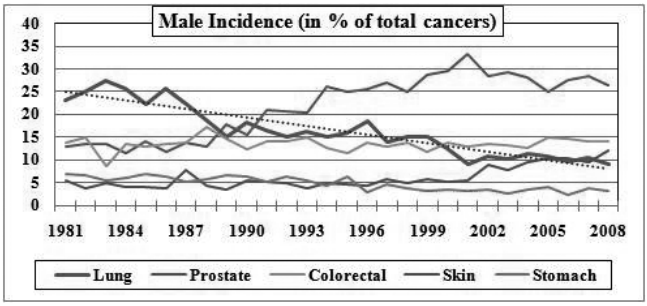

Figure 8: *Most Common Cancers in Males – Incidence (in % of total cancers)*

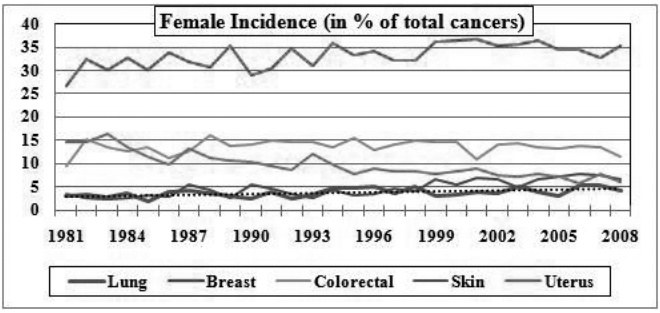

Figure 9: *Most Common Cancers in Females – Incidence (in % of total cancers)*

Breast cancer is by far the most commonly diagnosed cancer in women (Figure 9): twice as many cases as colon cancer, which is the second most common cancer in women. Lung cancer used to represent 3% of all cancers and now constitutes 5% of all cancers. Having been the 5th most common cancer in women, it has now become 4th most common cancer in women. Uterus cancer is on the decline. Skin cancer is on the rise and is approaching 10% of all cancers.

Most Common Cancers in Luxembourg – Mortality

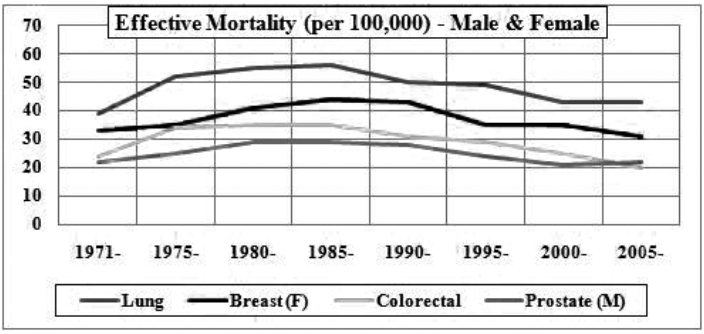

Figure 10: *(Taken from STATEC & modified): Effective Mortality (per 100,000) of most common cancers 1971–2009 in 5 year periods – Male & Female*

For the past 40 years, lung cancer has been the most common cause of cancer-related death in Luxembourg and it accounts for 20–25% of all deaths by cancer.

4. Discussion

Male incidences and mortalities have been decreasing over the last 28 years in Luxembourg. This decline in male incidences and mortalities is observed in almost every European country (9). What is different, however, is the rate at which lung cancer incidence, and consequently mortality, are decreasing in Luxembourg. The male ASR (W) regarding incidence, for instance, has halved from 60 in 1981 to

30 in 2008, compared to a 25% decrease in the Nordic countries from 40 down to 30 in the same time span (10). The Luxembourgish ASR (W) for incidence, which has been consistently higher than the ASR (W) in the Nordic countries at the end of the 20th century, has now come to a level with the Nordic countries and finally dropped below the world-wide estimate of 34 (12).

The available data did not go back far enough in time to allow us to draw any conclusions about the year when the incidences and mortalities peaked. It is probable that the peak occurred, similar to most European countries, around 1980 (9), i.e. must have occurred just before the period for which data on lung cancer incidence in Luxembourg exists.

The decline in lung cancer incidences in the male population from the 1980s onwards is most certainly due to the dawning of the cessation of smoking in the male population after the end of the Second World War and the publication of the Smoking and Health Report of the Advisory Committee to the Surgeon General of the United States in 1964. The latter was a milestone report that linked smoking and cancer and had lasting effects on smoking, i.e. reduced smoking and consequently lung cancer (13).

Female incidence and mortality rates in Luxembourg are, on average, twice as low as they are in Europe and the Nordic countries (9, 10). This allegedly consociates with the low prevalence of female smokers in the Luxembourgish population compared to European and Nordic female smokers. Both rates are still rising in 2008, an observation made across Europe, suggesting that efforts to stop female smoking from rising need to be made (14). The increase in lung cancer incidence in the female population can be related to marketing campaigns, which started in the 1920s and targeted women in particular, and an increased desire for equality in women.

What is unique and curious about the Luxembourgish lung cancer statistics is the fact that the mortality rate is higher than the incidence in both genders, which seems contradictory at first. In the Nordic countries, for example, the mortality is about 10% less than the incidence. (10) Considering 5-year survival rates are typically less than 10% (11), it seems logical that the mortality pattern, within a little, follows the incidence pattern. In Luxembourg, however, the mortality rate is about 25% higher than the incidence rate.

One hypothesis is that a part of the Luxembourgish population does not, in fact, get diagnosed in Luxembourg, but in other countries, for instance those with whom Luxembourg shares a common border, i.e. Germany, France and Belgium. These diagnoses slip indeed through the net and are not reflected in the statistics of the MTR, which solely holds information about cancers of Luxembourgish residents detected in Luxembourg. Moreover, in some obvious cases of cancer, anatomo/cyto-pathological or haematological examinations might just not be done for vari-

ous reasons, e.g. risk of spreading cancer further. Lastly, metastases of other cancers detected in the lung are occasionally misinterpreted as lung cancer, instead of being diagnosed correctly as metastasis of some other cancer. This can lead to the corruption of lung cancer mortality data and might result in apparently higher lung cancer mortality than incidence.

All these cases are reflected in the mortality data of Luxembourgish residents, however, which explains the curious particularity about the higher mortality than incidence in Luxembourg.

Age-specific rates are in good accordance with what is found Europe-wide and world-wide and confirm that lung cancer is most frequently diagnosed after the age of 60 (9, 10). From age-specific mortality, we see that there is a more significant peak in the male population, whereas the female mortality is wider and encompasses a wider span of age during which it is equally frequent. This might be due to the longer life expectation of females, which smoothens out the curve on the upper end in specie.

Overall, lung cancer remains the most common cause of death among all the cancers in Luxembourg, precisely because of the increased female lung cancer incidences. Comparing lung cancer with other cancers, this study found that, especially in males, lung cancer, being the most common cancer at the beginning of the 1980s, has now dropped to the 4th place behind prostate, colorectal and skin cancer. Possible explanations for the rise of prostate cancer are an increased number of medical exams undertaken by the 60+ male populations, better diagnostics, and a longer life expectancy.

On the female side, lung cancer is not among the most common cancers in incidence but remains, however, one of the most common causes of death by cancer. Uterus cancer incidence has been decreasing considerably over the last 28 years, due to an effective uterine testing from a young age, i.e. after first sexual experiences, which has been implemented in standard gynaecological exams in Luxembourg over the last decade. Hence, potential harms can be identified early on and preventive measures can be taken that reduce the risk of uterus cancer developing in females. Skin cancer is on the rise in both males and females and its evolution should be watched carefully.

A strong correlation between lung cancer and smoking has been firstly shown by Doll and Hill (15) and Wynder and Graham in 1950 (16). The tobacco industry vehemently opposed such studies. The Standing Committee of the tobacco manufacturers of Great Britain, in their 1957 report, attempted to deprecate and discredit Doll and Hill's investigation with arguments such as: "a contingent statistical correlation does not guarantee causation" (17). The major breakthrough in raising awareness about the causes of smoking was the publication of the Smoking and Health Report of the Advisory Committee to the Surgeon General of the

United States in 1964. The decline in smoking in the Western world was accompanied, contingently or causally, by a decline in lung cancer incidences. In the less developed world, however, tobacco industries are using the same strategies they used 100 years ago in the more developed world (18), i.e. depicting smoking as modern, liberating and empowering, to increase their market share.

From 2003 onwards, smoking is on the decline in Luxembourg: from 33% to 24% in 2010 (19). This could be related to the new law put in place in Luxembourg in 2006 (20), forbidding smoking in public places, which is going to be elaborated soon, further restricting smoking in Luxembourg (21). It is expected that stringent practice of this law will bring down both active and passive smokers leading to a decline in a lung cancer cases.

Finally, a word about what is missing in this study. It was not possible to come up with a rational estimate about the prevalence of lung cancer in Luxembourg, i.e. how many people live with it today, neither to obtain information about survival rates, e.g. 5-year survival rate, which are typically included in lung cancer statistics. For the Luxembourgish population, such statistics have not yet systematically been recorded by a register or institution. The way to obtain such information would involve consulting confidential medical data and death certificates.

Perspective

One common observation of all types of cancer is that cancer detected at advanced stages cause more death compared to those detected at early stage (22). The survival rate has been noteworthy when current therapies have been practiced on cancerous mass still confined to the organ of origin. Treating precursor lesion will help eliminate the invasive condition and hence prevent the progress of cancer (22).

The launching of a new electronic media records system in Luxembourg will enable capturing patient characteristics and treatments as well as track patient outcomes, creating a solid informatics infrastructure. Also, for the Luxembourgish population, the *personalized medicine* initiative will contribute by shifting all lung cancer cases to early detection and would significantly impact the overall mortality as well as the economic burden of the nation. Together, the improved data capture/management and the early-detection research would put Luxembourg on a new era of healthcare.

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A Clinical, Radiological and Computational Analysis of the Thrust Plate Prosthesis in Young Patients

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Abstract

Background and purpose: A thrust plate prosthesis can be used as an alternative to a conventional stem prosthesis, preserving the diaphyseal bone stock. Recent findings however predict a higher rate of aseptic loosening than with intramedullary devices. The purpose of our investigation was to compare the clinical outcome and radiological findings with a finite element analysis of bone remodeling. The hypothesis was that aseptic loosening after thrust plate prosthesis of the hip is inherent to the design.

Methods: From 1997 to 2001, 58 thrust plates were implanted in 52 patients. Average age at the time of surgery was 40.9 years. Ninety four percent returned for follow up at an average of 26 months. A finite element model of the thrust plate within the femur was developed and stress shielding as well as bone remodeling were analyzed.

Results: A total of 4 patients required revision surgery (6.9%). Data from the finite

element analysis revealed an inherent failure mechanism to the implant, facilitating stress shielding and loosening.

Interpretation: Lacking the ideal total hip prosthesis in young patients, the thrust plate can still be regarded as a feasible implant. However, surgeons and patients should be aware of possible mechanical problems regarding the design of the thrust plate. There is evidence that thrust plate prostheses are prone to early aseptic loosening. Clinical and radiological observations are in agreement with the results from the numerical simulations. Stress concentrations computed at the leash are interpreted as an explanation for leash pain. The authors regard computational methods as an aid to improve existing prosthesis design and future developments.

Author Key words: arthroplasty; thrust plate prosthesis; computational bone remodeling simulation; hip; finite element method.

Introduction

The Swedish National Hip Arthroplasty Register has revealed that active and young patients with posttraumatic osteoarthritis are at high risk for early revision surgery after total hip replacement. An implant minimizing bone stock loss at the initial procedure was thought to provide a theoretical advantage. A thrust plate prosthesis (TPP) that relies on metaphyseal fixation without violation of diaphyseal bone has been developed by Huggler and Jacob in 1978 (Figure 1A). The transfer of forces with this prosthesis has been reported to have similar biomechanical properties to the physiological state and to minimize bone remodeling in the proximal femur (Huggler and Jacob 1980, Huggler 1996). Although the thrust plate prosthesis has been in use since 1978, clinical reports are limited. Furthermore, revision rates seem to exceed those of intramedullary devices (Fink et al. 2000). In this context, stress-shielding is discussed, since it has been recognized as a general failure mechanism in total hip arthroplasty (Huiskes 1993, Jacob and Huggler 1980). Because stress-shielding explicitly depends on the prosthesis design, a design leading to minor stress-shielding is thought to be biomechanically more compatible. Current computational techniques based on a phenomenological constitutive theory are available to simulate stress distribution encountered from endoprosthetics and the related bone remodeling simultaneously (Beaupre et al. 1990, Nackenhorst 1997, Weinans et al. 1992]. Such tools enable qualitative studies on biomechanical compatible prosthesis design.

The purpose of this study was to evaluate the short-term clinical and radiographic outcome of the thrust plate prosthesis and to compare these findings with computational simulations on the stress-adaptive bone remodeling.

Patients and methods

Between 1997 and 2001, fifty-eight thrust plate prostheses (TPP) were implanted in 52 patients (33 male / 19 female) with an average age at time of surgery of 40.9 (SD 11.4) years. Twenty-five patients presented with posttraumatic osteoarthritis; the interval between injury and TPP implantation was 5.6 (SD 7.2) years. Thirteen patients suffered from avascular necrosis and twenty patients presented with primary osteoarthrits or dysplasia. Thirty-one patients had surgery prior to TPP implantation.

Surgery and Rehabilitation at Follow-up

The average surgery time was 135 (SD 56) minutes. On ten patients, additional procedures were performed, including hardware removal, resection of heterotopic ossifications, arthrolysis and neurolysis of the sciatic nerve. Postoperatively, patients were mobilized with partial weight bearing status for a period of six weeks. Clinical and radiological assessment were conducted regularly. In addition to a standardized radiographic assessment, anteroposterior fluoroscopy was performed by internally rotating the hip until the lesser trochanter just disappeared behind the medial cortex.

At follow-up, the following parameters were recorded: grade of osteoarthritis (Busse et al. 1972), preoperative grade of femoral head necrosis according to Ficat (Ficat 1985), inclination angle of the operated and the non-operated side, zones of radiolucency (Figure 1B) according to Fink (Fink et al. 2000), Harris Hip Score and heterotopic ossifications according to Brooker (Brooker et al. 1973).

Statistical Analysis

Statistical analysis was performed using computer generated SPSS for Windows. The level of statistical significance was set at $p < 0.05$.

Computational Studies on Biomechanical Compatibility

Computational techniques for the analysis of stress adaptive bone remodeling based on finite element models have been developed. Pioneer work in this field has been performed at the schools from Stanford (Beaupre et al. 1990) and Nijmegen (Weinans et al. 1992). Over the years, the theory and the algorithmic treatment have been enhanced continuously (Jacobs et al. 1995, Nackenhorst 1997). The finite element method is a well accepted tool for stress analysis. The basic assumption for the bone remodeling simulation is an evolution law, which describes bone formation in high stressed regions and atrophy in low stressed regions (Beaupre et al. 1990, Jacobs et al. 1995, Nackenhorst 1997, Weinans et al. 1992).

Numerous studies have been carried out for standard stem hip-joint prostheses, and the results are in good agreement with clinical observations (Figure 2). For total hip arthroplasty, it has been proven that primal effects can be efficiently studied by quasi three-dimensional finite element models. Although the finite element mesh is 2-dimensional, a 3-dimensional load bearing behavior is modeled by superposition of a so called side plate and properly adapted thickness of the elements (Nackenhorst 1997).

The first step of these calculations is the set up of a biomechanical equilibrated femur model. By optimization strategies, the statically equivalent loads, i.e. joint and muscle forces, are adapted in a way that the resulting bone mass density distribution reflects the physiological structures. In these studies, distributed statically equivalent loads with resultants of 700 N for the abductor muscle and 2300 N for the joint load, acted at angles of 62_o and 66_o with respect to the horizontal plane. In figure 3, the computed bone mass density is compared to a radiograph. The typical trabecular structures are clearly obtained by the simulation. It is remarkable that these characteristics, i.e. the development of the medullary canal and the trabecular structure of the cancellous bone have been computed from an initially homogenous topology.

In this equilibrated femur model the prosthesis is implanted virtually (Figure 4) while the loading conditions are kept constant. For simplicity, a perfect bond between bone and prosthesis due to ossification at the finished surfaces of the prosthesis has been assumed postoperatively. Various parameter constellations have been carried out by these simulations. Thus, the material properties of the TPP have been varied between steel and titanium and the influence of pre-stressing of the central bolt has been studied.

Results

Functional Results

Out of 58 thrust plate prostheses, 54 implants (49 patients) remained in situ until the latest follow-up (93% survivorship). Postoperative clinical and radiological status was obtained for 51 implants. The average follow-up for these fifty-one cases was 26 (SD 11) months. A significant relief of pain was achieved in 45 out of 51 cases (88%). In 47 cases (92%), the patients stated that they would undergo the procedure again. The median Harris-Hip-Score was 73 (SD 20.5) with no significant difference between the different groups as analyzed by the Post Hoc Test. The average Body-Mass-Index was 26.8 (SD 5.2). This finding significantly correlated with a low Harris-Hip-Score ($p=0.027$). The average postoperative hip pain, as graded on a pain scale from zero to ten, was 2.5 (SD 2.1) and did not significantly differ between the diagnosis groups (Kruskal-Wallis). The average lateral thigh

pain ("leash pain") was graded as 3.2 (SD 2.7) and was noted in 40 cases. There was no significant relationship between leash pain, Body-Mass-Index (p=0.30), and length of follow-up respectively (p=0.56).

Radiological Results

The average postoperative inclination angles on the non-operated side (133.04° ±6.4°) and the operated side (132.96° ± 6.3°) were similar. Patients with an inclination angle between 125° and 135° had significantly lower hip pain than the rest of the series (p=0.046, Mann-Whitney-U Test). The post-operative Harris-Hip-Score also trended higher in patients with a postoperative inclination angle between 125° and 135° (74.8° ± 19.7°) as compared to 64.6° ± 21.3° in the rest of the series.

However, this difference was not statistically significant (p=0.11, t-Test). At follow-up, radiolucencies were noted in seven cases. Due to minimal extent, limited progression and mild clinical symptoms, a revision was not considered in those patients (Table 1). Post-operatively, heterotopic ossifications were noted in 21 cases and were classified as grade 1 (n=13), grade 2 (n=5), and grade 3 (n=3) according to Brooker.

Revision Surgery

4 patients (6.9%) required a revision total hip arthroplasty: Three patients never experienced postoperative pain relief. For those three patients, it was assumed that the postoperative osseous integration of the implant had failed. One patient with multiple hip dislocations required revision surgery. Secondary loosening of a previously integrated implant was not recorded in this series. Additional complications included postoperative hip dislocations (5 patients). Other complications that required surgical intervention were: trochanter bursitis (n=2), fistula (n=1) and seroma (n=1).

Computational Studies on Biomechanical Compatibility

The simulation immediately gave an impression regarding the force flow due to the prosthesis. In figure 4, the principal interaction of forces are sketched by the arrows. It is easily understood that the TPP acts like a simple supported cantilever beam with the joint load being supported by the medial cortex at A and the bending moment mainly taken up by the lateral plate and screws at B. In vivo, the loading is dynamic. However, considerable tensile joint forces F do not occur at all. Therefore, the forces do not change from compression to tension and vice versa. It is obvious that the region proximal to the prosthesis is stress-shielded leading to the atrophy of the cancellous bone as shown in figure 5. The mass density distribution after a certain period of time of remodeling (Figure 5 B) is compared

with the postoperative state (Figure 5 A). Furthermore, the simulations indicate a loss of bone mass density immediately under the thrust plate, proximal as well as distal. This indicates that this device ensures primary stability only, whereas at later stages of remodeling the load transfer is controlled by the bone under a more physiological configuration.

The influences of several parameter variations are depicted in figure 5 C and 5D. The effect of pre-stressing (800 N) enforced by the central bolt during surgery is shown in figure 5 C in comparison with figure 5 B. According to Schreiber, the prestressing is for primary stability and vanishes after a certain time, a statement which is supported by the simulations. Thus, pre-stressing has no influence on the long term behavior of stress-shielding and bone remodeling. Furthermore, the effect of reduced stiffness of the device by use of a parameter set for titanium instead of steel is depicted in figure 5 D. The stiffness properties of titanium are only one half of those from steel whereas the mechanical limit strength is similar. As expected, the amount of bone remodeling for titanium parameters is not as drastic as that of steel. However, stiffness reduction does not change the global load bearing behavior and does not seem to improve the endurance of the system.

Discussion

The theoretical advantage of the TPP is the preservation of the diaphyseal bone stock and the avoidance of bone remodeling in the proximal femur. In a biomechanical setting, physiological loads on the proximal femur have been recorded, thereby suggesting a reduced bone remodeling. Shear stresses between the thrust plate and the cortices of the femoral neck are thought to contribute to the osseous integration of the thrust plate. To ensure near physiological loads on the proximal femur, the TPP should be implanted with an inclination angle of 125° to 135°. Implantation of the TPP in either varus or valgus position leads to shear stress, deviation of the plate at the lateral femur, decreased range of motion, and unphysiological loads on the proximal femur. Overall, a valgus position of the TPP seems to be less disadvantageous than a varus position (Huggler 1996, Jacob 1996). The results in this study revealed the paramount importance of a correct inclination angle since patients with an inclination angle of 125° to 135° trended towards higher Harris-Hip-Scores and had significantly less hip pain.

Functional Results

In this series, 88% of the patients experienced subjective improvement and 92% of the patients stated that they would undergo the procedure again. The residual pain on a visual analog scale averaged at 2.5. Despite these results, the average Harris-Hip-Score tended to be lower compared to previous reports in this field (Fink et al. 2000, Fink et al. 2002). Possible explanations for this observation

might be the relatively young age and the high number of previous surgeries. For these patients, a less favorable outcome following total hip arthroplasty has been reported (Havelin et al. 1994, Johnsson et al. 1988, Malchau et al. 1993). In addition, the follow-up period in this series was shorter than those recorded in previous series. This time period becomes of importance considering other series that have described a continuity of increasing Harris-Hip-Scores after two years following TPP implantation (Fink et al. 2000, Fink et al. 2002).

The problem of leash pain following TPP implantation is specific for this type of prosthesis. It has mainly been observed in young and lean patients and it tends to decrease with time. Although the design has been modified in 1986, still a considerable number of patients experience leash pain, which can be of major complaint (Jacob 1996). In this series, however, leash pain did not correlate with a low Body-Mass-Index or a short follow-up period. Therefore, we recommend that this problem should be discussed with the patient before surgery.

Radiological Results

The post-operative inclination angle varies according to the rotational position of the hip joint. The area below the thrust plate representing zone 1 and 2 is only visible with perpendicular projection of the thrust plate. This view can be obtained between 10 and 20º internal rotation of the lower limb (Gruber et al. 1997). The evaluation of the inclination angle demonstrated that 94% of the patients were within the physiological range of 120 to 140º. An average inclination angle of 133º can be considered highly satisfactory. Similar results were obtained in previous studies (Fink et al. 2000, Fink et al. 2002).

Regarding radiolucencies, the data in the literature is limited. Fink et al. found radiolucencies in 12.6% of the patients with a TPP (Fink et al 2000). In this series, 13% of the patients had radiolucencies at follow-up. In these cases, the radiolucencies were mostly localized and measured 1mm of width. It is believed that non-progressive radiolucencies without any signs of migration of the hip prosthesis are not necessarily a sign of loosening, but rather a sign of localized fibrous reactions (Engh et al. 1990, Herren et al. 1987). Heterotopic ossifications were found in 41% of the cases. In a prospective multicenter study including 6000 total joint arthroplasties, Müller and Koch found heterotopic ossifications in 38% of the cases with previous surgeries. Decreased range of motion, femoral head necrosis, posttraumatic osteoarthritis and postoperative hematoma were identified as risk factors. A significant number in this series had some of these risk factors for the formation of heterotopic ossifications.

Revision Rate and Complications

The revision rate in this series was 6.9% and is comparable to previous reports in regards to TPP (Table 2) (Fink et al. 2000, Fink et al. 2002). On the other hand

it is higher in comparison to the results of the Norwegian / Swedish Arthroplasty Register (Havelin et al. 1994, Johnsson et al. 1988, Malchau et al. 1993). However, comparing these results, age of the patients at the time operation is considered an important factor because patients included in our series were extremely young. The revision rates for young patients undergoing total hip arthroplasty have been reported to be higher than those in older populations, ranging from 4.5 to 12% after 4.5 years (Havelin et al. 1994).

Another problem observed in this series was an unsatisfactory postoperative dislocation rate. Comparing the results obtained in this study with previous reports, it has to be considered that the majority of patients in this series have undergone previous hip surgeries. Woo and Morrey (1982), who reviewed a series of 10,500 total hip arthroplasties, reported a dislocation rate of 5% for patients who have undergone previous hip surgeries. Although the precise reason for this phenomenon is unknown, it must be assumed that soft tissue damage, scar tissue, and muscular imbalance contribute to increased dislocation rates in patients with prior hip surgery.

Computational Analysis

The simulations have shown that in comparison with standard stem hip-joint endoprosthesis, the thrust plate prosthesis provides a more physiological load transfer (Figure 2 and Figure 5). This is demonstrated by the absence of stress shielding in the diaphyseal femur. However, the cancellous structure of the metaphysis does undergo stress-shielding which leads to atrophy in this domain. Failed osseous integration and loss of stability are the results. This finding has been reported previously (Fink et al. 20009. Radiolucency observed above the prosthesis and under the thrust plate indicates non-integration caused by missing mechanical stimulation.

The load at the lateral plate is mainly transferred by the screws, which causes a relatively high stress concentration. This finding partially explains the high incidence of leash pain observed in TPP.

Conclusions

Still lacking the ideal total hip prosthesis in young patients, the TPP can be regarded as a feasible implant. However, the surgeon and the patient should be aware of the occurence of early loosening in regards to the design of the TPP. Finite element analysis underlines these clinical findings and is likely to assist in the development of new metaphyseal fixed hip prostheses in the future.

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Tables

Table 1

Radiolucency under the thrust plate.

Diagnosis	Radiolucency Zone	Width of radiolucency	Age	Follow-up [months]	Harris-Score
Post-inflammatory OA	5	2mm	21	26	88
OA secondary to dysplasia	3	1mm	43	18	86
OA secondary to dysplasia	5	2 mm	47	16	47
Avascular necrosis	5	1 mm	36	19	100
Avascular necrosis	5	1 mm	21	33	89
Post-traumatic OA	2	2 mm	47	18	54
Post-traumatic OA	1, 2	both 1 mm	36	24	80

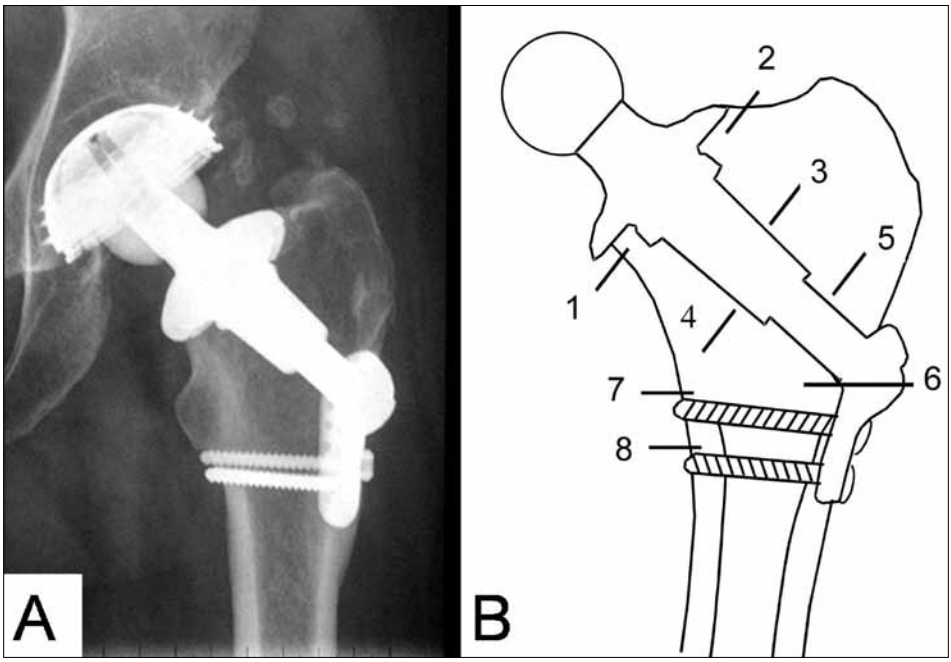
OA = Osteoarthritis

Table 2

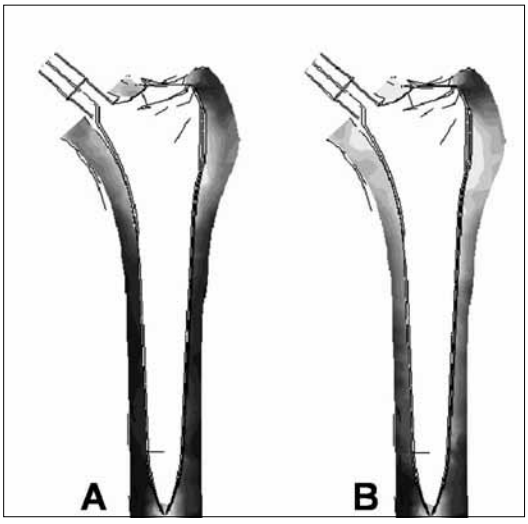
Revision rates following implantation of the thrust plate prosthesis.
A literature review.

Author	N	Indication	Age	Follow-up	Revision rate
Huggler 1993	115	Miscellanous	53	max. 9 y	21%
Fink 2000	47	Rheumatoid arthritis	41	∅ 2.2 y	15%
Fink 2002	72	Avascular necrosis	47	∅ 4.8 y	8.3%

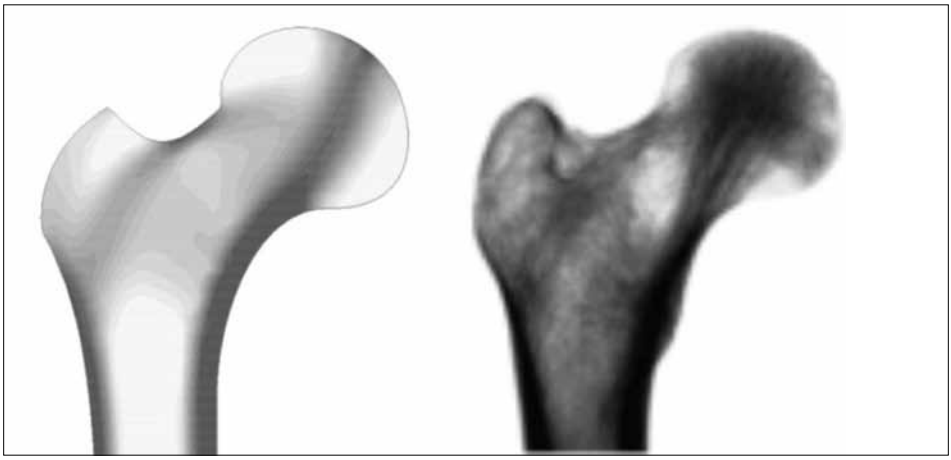
Figures



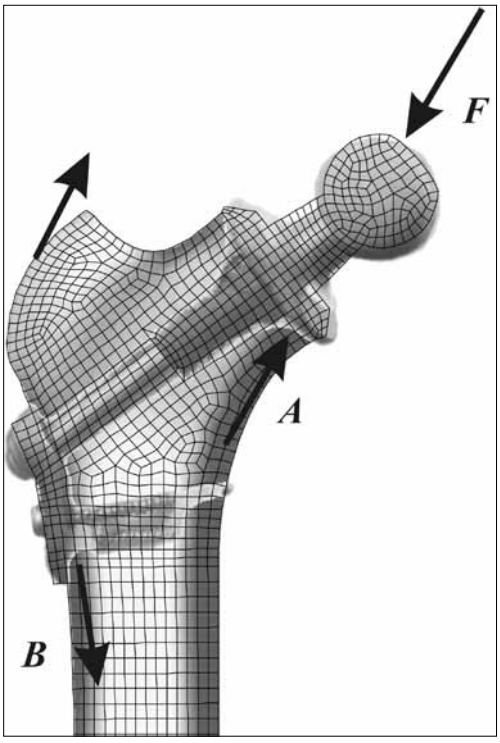
A: Fifty year-old female patient, thirty-six months following total hip arthroplasty using the thrust plate;
B: Zones of radiolucencies under the thrust plate;



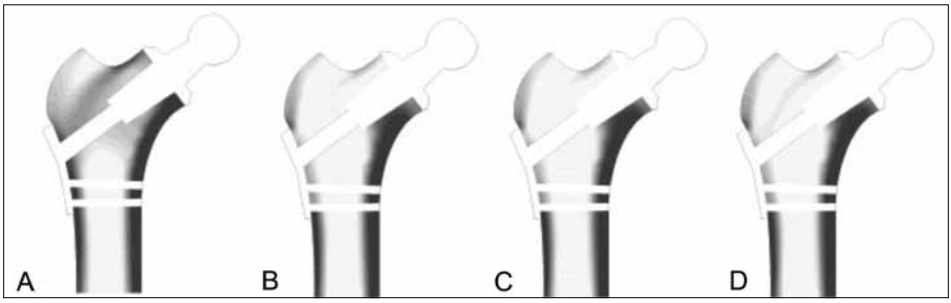
Computed bone-remodeling caused from a classical stem-endoprosthesis;
A: post-operative bone-mass density distribution;
B: long-term configuration.



Radiological and computed average mass density of the proximal femur.



Finite element model of the human femur with TPP-prosthesis; the arrows indicate loading and interaction forces.



Bone remodeling caused from the TPP in dependence of construction parameters;

A: post-operative stage;
B: steel-prosthesis;
C: steel-prosthesis with pre-stressed central bold;
D: titanium-prosthesis.

Vignette historique
Menschenfett

In einer Zeit, in der in unseren Kliniken tagtäglich Fett hier abgesaugt und dort eingespritzt wird, um das Aussehen von Patienten zu verändern, denkt man unwillkürlich an jenen anderen Handel der Henker und Apotheker mit Menschenfett

• • •

1869 schreckte eine Nachricht das luxemburger Publikum auf:

> „Das „Correspondenzblatt der ärztlichen und Pharmazeutischen Kreisvereine in Sachsen“ bringt die Notiz, dass die „pommade de Lyon“ Menschenfett aus den Pariser Anatomien sei“[1].

Menschliches Fett in einer französischen Salbe? Offiziell enthielt die Lyon'er Salbe, glaubt man dem „Dictionnaire de médecine, de chirurgie, de pharmacie, des sciences“ von Isidore Bricheteau, Joseph Briand und Ossian Henry (Bruxelles, 1834), aus „oxyde rouge de mercure porphyrisé“ und „pommade rosat“ – alles hochanständige Chemikalien. Eingesetzt wurde die Salbe in der Behandlung von Entzündungen der Augenlider[2].

In der Region von Jena kannte man wohl „Menschenfett“ – doch handelte es sich dabei um ein Dorfbier, von dem man sich erzählte, dass das Brauwasser unterirdisch über einen Friedhof geflossen war. War Frankreich also besonders rückständig? Oder war das Inserat doch nur Teil einer geschickten Stimmungsmache gegen Frankreich? Schon 1838 finden wir eine ähnlich abscheuliche Anspielung auf Frankreich in einer deutschen Schrift:

> „Wie nöthig indess von Seiten der Behörden eine strenge Beaufsichtigung der Amphitheater[3] war, geht unter andern aus der Thatsache hervor, dass die Anatomiewächter Jahre lang einen förmlichen Handel mit Menschenfett getrieben, und besonders an die Emailleurs und Verfertiger falscher Perlen in bedeutenden Mengen, das Pfund bis zu 17 Sols, verkauft hatten, und dass bei der Illumination zur Feier der Vermählung Napoleons mit Marie Louise die Lampions am Gebäude der medizinischen Facultät und dem Pallaste Luxemburg mit Menschenfett, dem etwas Talg zugesetzt war, gefüllt waren“[4].

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[1] „Luxemburger Wort” vom 3.4.1869.

[2] Hannoversche Annalen für die gesammte Heilkunde, Hannover 1838, Band 3 erstes Heft S. 573

[3] Sano, Magazin für Patienten, Gäste und Mitarbeiter der Kärntner LKH, Nummer 7 / 2008 S. 20.

[4] Janine Kopp, Hingerichtet, einbalsamiert und als Medizin verkauft, in: UniLu(zern) Aktuell, Ausg. N°35 Februar 2011.

Und wenn schon! Alle erdenklichen Fette wurden im Mittelalter benutzt: Fette (pinguedo) von „feuchten" Tieren wie den Schweinen, Fette (adeps) von „trocknen" Tieren, wie dem Rind. Kein einziger Chirurg des Mittelalters aber gebrauchte Menschenfett – viel zu gross wäre die Gefahr gewesen, als Hexer angeklagt zu werden! Ausnahmen bestätigen diese generelle Zurückhaltung: so besorgten im späten 14. Jahrhundert zwei Hebammen (Perrette aus Rouen und Catherine La Petioune) einer Frau den Körper einer Totgeburt, damit mit dem daraus gewonnenen Fett das Gesicht eines von Lepra befallenen Edelmann behandelt werden konnte. Beide wurden vor Gericht angeklagt[5].

Später schwand das Tabu, und man liest vom freimütigen Gebrauch des Menschenfettes. Seit dem 16. Jahrhundert wird Menschenfett in Arzneibüchern unter dem Namen „Pinguedo hominis" (für unbehandeltes, rohes Fett) oder „Axungia hominis" (für ausgelassenes Fett resp. Schmalz) erwähnt, als wichtiger Bestandteil hochwertig erachteter Salben und anderer fetthaltiger Arzneiformen. Als besonders heilkräftig galt Fett aus dem Körper einer rothaarigen Frau[6].

Der französische Arzt Antoine Mizaldus (1520–1578) schwor auf Menschenschmalz bei der Behandlung von schmerzenden Gliedern. 1640 wurde in Kopenhagen der Bericht einer wundersamen Heilung veröffentlicht – eine hinkende Frau hatte Fett von einem menschlichen Beinknochen sowohl gegessen als auch ihr lahmes Bein damit eingerieben – und war binnen 2 Tagen geheilt worden[7]! 1663 schrieb der in Mainz tätige Professor der Medizin Johannes Joachim Becher (1635–1682): „Zerlassen Menschenfett ist gut für lahme Glieder, So man sie damit schmiert, sie werden richtig wieder"[8]. Aus Gründen der Analogie wurde es vor allem bei den als „kalt" und „zehrend" verstandenen Erkrankungen wie Gicht und Arthrose, Tuberkulose und Anämie angewandt; im Wutachtal im südlichen Schwarzwald galt es gar als Allheilmittel, als „Panazee".

Fett wurde nicht nur äusserlich angewandt. Hier ein Bericht mit Einnahme des Fettes. Der Unternehmer Gottfried Greiner aus Limbach (1732–1797) suchte den „berühmten Doktor" Ness auf. Dieser diagnostizierte eine Krankheit „auf den Tod" und verschrieb Menschenfett, das er aus der Leiche einer jungen hingerichteten Kindsmörderin selbst ausgekocht hatte[9]. Greiner graute es, das Mittel einzunehmen und zog Muttermilch vor …

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[5] Johann Bartholomäus Trommsdorff, Handbuch der pharmaceutischen Waarenkunde, Erfurt 1806 S. 573.

[6] Sano, Magazin für Patienten, Gäste und Mitarbeiter der Kärntner LKH, Nummer 7 / 2008 S. 20.

[7] C.C. Petersen, in: Revue d'Histoire de la Pharmacie 1959 Vol 47 n°163 S. 223.

[8] Janine Kopp, Hingerichtet, einbalsamiert und als Medizin verkauft, in: UniLu(zern) Aktuell, Ausg. N°35 Februar 2011.

[9] Barbara Duden, Geschichte in Geschichten: ein historisches Lesebuch, Campus-Verlag 2003 S. 295.

„Man hält übrigens das Menschenfett für schmerzstillend, erweichend und zertheilend. Einige Aerzte rathen es innerlich zu nehmen in abzehrenden Krankheiten, und zu Zertheilung des geronnenen Geblüts. Sonst aber wird es nur äußerlich gebraucht wider Flüsse, Zittern der Glieder und Lähmungen. Man bedient sich desselben auch in Beinbrüchen, Verrenkungen und Quetschungen der Nerven und Sehnen. Eine Salbe aus Menschenfett und Vitriol=Spiritus soll ein vortreffliches Mittel gegen die Trockenheit und Sprödigkeit der Glieder seyn“[10].

Wie aber an menschliches Fett herankommen, wenn die Kirchen die Unversehrtheit der Leichen forderten? In Schwaben wird das aus Gräbern geholte Leichenfett „alt aih“ (= Altee) genannt (Knoblauch-Matthias, Handwörterbuch des deutschen Aberglaubens, Berlin 1933 S. 106). In der Praxis stammte Menschfett meist von Menschen ohne Religion und ohne Verwandte – von Vagabunden. In Kriegszeiten verschwand vermutlich mancher Tote nicht in dem Massengrab, sondern im Siedekessel eines „heilenden Henkers“. Hielt man auf das Fett normal verstorbener Menschen grosse Stücke, so steigerte sich die Erwartung bei gewaltsam zu Tode gekommenen Zeitgenossen ins Unermessliche. In der Tat umgab die Verletzten seit der Antike eine Aura des Wunderbaren. Kaisergattinnen, die Gladiatorenblut tranken usw.

Hauptlieferant des Apothekers waren, abgesehen von Grabschändern und Mördern, im Wesentlichen die Henker. Anders als die Totengräber, die einen würdevollen Umgang mit denihm anvertrauten Leichen pflegten, hatten die Henker Zugang zu entehrten Leichen. Niemand schritt ernsthaft ein, wenn Teile dieser Leichen – etwa der Daumen oder die Knochen eines Diebes (Schelmbein) – abhanden kamen. Oft wurde das Amt des Henkers aus praktischen Gründen mit dem des Abdeckers zusammengelegt. Da Abdecker die Produkte ihrer Arbeit selbst verwerten durften, verfügten sie „wie selbstverständlich“ unter anderem über „axungia canis“, Hundeschmalz, welches zur Salbung entzündeter Gelenke bei Pferd und Mensch zum Einsatz kam. Scharfrichter ihrerseits, oft Abdecker und Chirurg in einer Person, sicherten sich ein zusätzliches Einkommen durch die Herstellung und den Verkauf von besonders wertvollen, heilmagischen Substanzen, die aus den Körpern von Hingerichteten gewonnen wurden. Abgeschlagene Daumen verhinderten die „Ebbe“ im Portemonnaie, mit der „Toten Hand“ wurden Feuermale, schmerzende Zähne, Überbeine und bösartige Tumoren berührt, in der Hoffnung, das Leiden auf die Hand zu bannen. „Arme-Sünder-Fett“ nannte man Fett, das aus den Leichen von Menschen gewonnen wurde, die hingerichtet worden waren – deren Seele folglich verdammt war da ihnen, ebenso wie den Selbstmördern, ein christliches Begräbnis versagt blieb: daher der Zusatz „arm“. Da die Bestattung von Verbrechern und von Selbstmördern ohne kirchliche Kontrolle in

[10] J.G- Krünitz, Oeconomische Encyclopädie, 1773 – 1858.

nicht geweihter Erde und ohne Zeremoniell erfolgte, bot sich den Henkern und ihren Knechten reichlich Gelegenheit, Teile dieser Körper zu entfernen – Finger, Hände, Blut, Fett. Zumeist erfolgte der Handel mit diesen Teilen am Rande der Legalität – die Käufer schlichen im Schutze der Nacht zum Hause des Henkers und erwarben die begehrte Ware wortwörtlich auf dem „Schwarzmarkt". Nur selten liest man von einer behördlichen Genehmigung, so 1613, als der Rat der tschechischen Stadt Eger dem Scharfrichter die Erlaubnis erteilte, das Fett von einem Gehängten abzunehmen „weil davon vielen Menschen Hüllf geschehen kann". 1707 gestattete der Rat der Stadt Luzern dem Apotheker Georg Adam Schmid „Schmaltz aus dem Ruggen aber nit weiteres" aus dem Rücken der hingerichteten Cathry Weber zu entfernen.

Fette Leichen waren ergiebig, aus dürren war nur wenig herauszuholen – der Schweitzer Medizinprofessor Tobias Andreas gewann 1675 aus dem Körper einer ertränkten Kindsmörderin 40 Pfund Fett. Neben Armsünderfett von Hingerichteten, Knochenmehl und Hirnschalenmoos standen diverse Absonderungen des menschlichen Körpers wie getrockneter Speichel, Nasenschleim, Schweiß, Sperma, Ohrenschmalz, Menstrualblut, Nachgeburtsteile und Mumienpulver in den Regalen der Apotheken zur Disposition. Diese galten ebenfalls als wirksame Heilmittel und wurden in den Destillierbüchern des 15. bis 17. Jahrhunderts empfohlen.

Die Dresdner Medizinaltaxe von 1761 listete Menschenfett unter den zu handelnden Arzneien, dasselbe taten noch im 19. Jahrhundert mehrere Pharmakopöen[11]. Neben gemeinem Menschenfett fand zunehmend Kinderschmalz breite Verwendung, vor allem bei Migräneattacken und nächtlichen Wadenkrämpfen ...

Mit heilmagischer Bedeutung wurde „Armsünderfett" resp. „Armsünderschmalz" in der Volksmedizin bis in das 19. Jahrhundert von Scharfrichtern aus den Körpern von Hingerichteten hergestellt und verkauft. Dabei wurde gelegentlich geschummelt. Lesen Sie von Balzac die 1830 erschienenen „Mémoires de Sanson" – Sie werden erfahren, dass der berühmte Henker Schweineschmalz aus der Metzgerei besorgte und in Töpfchen umfüllte, die er mit rotem Papier abdeckte und als Menschenfett verkaufte

Das luxemburgische Wörterbuch kennt eigenartigerweise den Begriff „Armesönnerfett" nicht, wohl aber denjenigen „Armesönnerklack" für die Glocke, die für den zum Tode Verurteilten geläutet wurde, während er zur Richtstätte gebracht wurde.

Hier die Werbung, die das „Luxemburger Wort" am 26.1.1950 für ein neuzeitliches Rheumamittel abdruckte:

[11] Johann Bartholomäus Trommsdorff, Handbuch der pharmaceutischen Waarenkunde, Erfurt 1806 S. 573. Pharmacopoea universalis, Weimar 1832 S. 69.

„Rheumatiker … das Fett eines Gehenkten. Im siebzehnten Jahrhundert gebrauchten unsere Vorfahren ein seltsames Mittel gegen den Rheumatismus: das Fett eines Gehenkten. Dies Mittel war aber schwer zu bekommen! Seine Wirksamkeit schien fürwahr um so grösser zu sein, als es eine Seltenheit war. In Paris drängte sich immer am berühmten Galgenhügel Montfaucon eine Menge von Rheumatikern, die dem Henker ein wenig von diesem wertvollen Fett abbettelten, womit sie dann ihre schmerzhaften Glieder gründlich einrieben. Das Mittel war nach kurzer Zeit so begehrt, dass bald – wie später aus diesen Aufsätzen erhellen wird mit dem — Menschenschmalz ein sehr sonderbarer Handel getrieben wurde. Es ist dies der Anlass, alle Rheumakranken daran zu erinnern, dass sie in unserer Zeit über ein bewährtes, zweckmässiges Mittel gegen ihre Qual verfügen: ein oder zwei „WEISSE KREUZE“ genügen“ (Bild).

… und wieder taucht in diesen Zeilen der Name einer französischen Richtstätte auf als Quelle des begehrten Fettes. Montfaucon, der Hügel der Falken, auf dem seit die Parisr ihre Verbrecher hinrichteten. Wenn Sie sich bei Ihrem nächsten Parisbesuch auf die Kreuzung Quai des Jammapes /rue de la Grange-aux-Belles verirren, sollten Sie wissen, dass hier seit dem 13. Jahrhundert der Galgen Montfaucon stand, an dem so viele ihr Leben beschlossen. Als man im frühen 17. Jahrhundert das „Hôpital St. Louis“ ganz in der Nähe erbaute, wurde der Galgen aufgegeben und schliesslich um 1760 abgerissen. Doch kann man noch heute in Haus 57 der rue de la Grange-aux-Belles das Rasseln der Ketten der Verurteilten hören. Ihr Fett aber kann man in Medizinmuseen[12] betrachten: es füllt die Töpfe mit jener mysteriösen Aufschrift „Axungia hominis“.

Dr Kugener H.

[12] Deutschen Apothekenmuseum im Heidelberger Schloss, Schweizerisches Pharmaziehistorisches Museum in Basel, Totengäßlein 3.

La pubalgie du sportif
6e symposium annuel de médecine du sport
D'Coque, 3.12.2011, 8.45 – 14.00 hrs

Organisateurs:

- Société Luxembourgeoise pour la Recherche en Orthopédie et en Médecine du Sport
- Laboratoire de Recherche en Médecine du Sport – CRP-Santé
- Centre de l'Appareil Locomoteur, de Médecine du Spoprt et de Prévention – CHL
- Département Ministériel des Sports

Communiqué de presse:

Au congrès de Médecine du Sport organisé par le Comité International Olympique en 2011 à Monaco, la pubalgie du sportif a été reconnue comme une des grandes énigmes des pathologies en médecine du sport[1]. C'est une des raisons pour lesquelles les organisateurs luxembourgeois ont choisi ce sujet comme thème principal de leur 6e édition du symposium de fin d'année. Désormais traditionnels, ces rendez-vous ont été instaurés à un rythme annuel depuis la création du service de médecine du sport au CHL – Clinique d'Eich en 2004. Ils s'adressent à un public multidisciplinaire: médecins du sport, kinésithérapeutes, ostéopathes, entraîneurs voire athlètes et dirigeants sportifs pourront ainsi profiter des débats initiés par des experts nationaux et internationaux.

Le programme prévoit une mise au point complète de la pubalgie du sportif, allant d'une description générale illustrant les causes musculaires et ostéoarticulaires par le Dr. Christian Nührenbörger (CHL-Clinique d'Eich). Le Dr. Frédéric Walter (radiologue, CHL-Clinique d'Eich) passera en revue l'imagerie nécessaire. Il sera suivi du Dr Sascha Hopp de l'Université de la Sarre qui présentera les causes d'ostéite pubienne et leurs traitements avant qu'un débat franco-germanique opposera 2 chirurgiens très reconnus dans leurs pays respectifs, à savoir le Dr Jens Krüger de Berlin et le Dr. Lutz de l'Université de Strasbourg qui présenteront leur expérience chirurgicale. Le rôle de l'articulation de la hanche dans l'origine des pubalgies et les nouvelles possibilités de chirurgie arthroscopique sera présenté par le Prof. Romain Seil (CHL – Clinique d'Eich). Enfin, le Dr. Per Hölmich[2] de Copenhague, un des pionniers du traitement non-chirurgical du problème, présentera les dernières trouvailles de son groupe d'étude [3,4,5].

En fin de symposium, l'équipe de kinésithérapie du CHL-Eich aidée par des experts danois montrera les nouveaux exercices de prévention aux intéressés dans des séances pratiques. À noter que les exposés seront donnés en allemand, français

et anglais et que les diapositives seront exclusivement en anglais. La participation aux frais est de 25 €. Une inscription préalable n'est pas requise.

Dr. Christian Nührenbörger
Prof. Romain Seil

[1] Engebretsen L.: The groin enigma in sports. IOC World Conference on Prevention of Injury & Illness in Sport. April 2011, Monaco.

[2] Hölmich P, Uhrskou P, Ulnits L, Kanstrup IL, Nielsen MB, Bjerg AM, Krogsgaard K. Effectiveness of active physical training as treatment for long-standing adductor-related groin pain in athletes: randomised trial. Lancet. 1999 Feb 6; 353 (9151): 439–43.

[3] Thorborg K, Serner A, Petersen J, Madsen TM, Magnusson P, Hölmich P. Hip adduction and abduction strength profiles in elite soccer players: implications for clinical evaluation of hip adductor muscle recovery after injury. Am J Sports Med. 2011 Jan; 39 (1): 121–6. Epub 2010 Oct 7.

[4] Thorborg K, Hölmich P, Christensen R, Petersen J, Roos EM. The Copenhagen Hip and Groin Outcome Score (HAGOS): development and validation according to the COSMIN checklist. Br J Sports Med. 2011 May; 45 (6): 478–91.

[5] Hölmich P, Nyvold P, Larsen K. Continued Significant Effect of Physical Training as Treatment for Overuse Injury: 8- to 12-Year Outcome of a Randomized Clinical Trial. Am J Sports Med. 2011 Aug 3. [Epub ahead of print]