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EDITORIAL

Stroke prevention in atrial fibrillation

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ABSTRACT

The only major and potentially fatal risk for patients with atrial fibrillation is the development of systemic thromboembolism. Stroke occurs five times more frequently in patients with atrial fibrillation than in comparable patients in sinus rhythm. The yearly incidence of stroke in atrial fibrillation largely depends on the underlying heart disease: from 0.5% in 'lone' atrial fibrillation up to 20% in rheumatic heart valve disease.

Oral anticoagulation with vitamin K antagonists dramatically reduces the stroke risk by two-thirds, but is a laborious and patient-unfriendly therapy. Oral direct thrombin blockers and oral factor Xa antagonists, both without therapy monitoring, may replace warfarin for this indication, but there are safety and efficacy issues to be resolved. Oral antiplatelet agents are effective, but clearly less than warfarin. Angiotensin receptor blockers are currently under investigation.

Routine electrocardioversion for atrial fibrillation does not reduce the stroke risk, but promising techniques include electroablation of the left atrium and occlusion of the left atrial appendage.

KEYWORDS

Aspirin, atrial fibrillation, cardioversion, stroke, warfarin

The yearly incidence of stroke in patients with atrial fibrillation is about 5%,[1] which is five times higher than in comparable populations in sinus rhythm. The stroke risk largely depends on the underlying heart disease. In 'lone' atrial fibrillation (absence of heart disease), the stroke risk is only 0.5% per year,[2] whereas in atrial fibrillation associated with rheumatic valvular heart disease such as mitral valve stenosis it is very high. Needless to say, oral anticoagulation (with warfarin, acenocoumarol and phenprocoumon) has shown to be effective in the prevention of thromboembolism in patients with valvular and nonvalvular atrial fibrillation.[3] Severe bleeding with warfarin is seen in one in 100 patients per year, which is double the risk of stroke in lone atrial fibrillation. Therefore, anticoagulation is only indicated in atrial fibrillation patients with a stroke risk of 2% or more per year.

For several decades oral anticoagulants have been used in the treatment and prevention of venous thrombosis. Oral anticoagulants block the vitamin K dependent liver production of the plasma clotting factors II (prothrombin), VII, IX and X. They have a relatively narrow therapeutic window which requires close international normalised ratio (INR) monitoring: overdosing may result in life-threatening bleeding and underdosing in inefficacy. Recently, some major improvements in the monitoring of oral anticoagulation have been made: efficacy and safety of oral anticoagulation were found to be correlated with the INR values reached in trials in patients with atrial fibrillation,[4] in those with artificial heart valves[5] and in those after myocardial infarction.[6] Moreover, INR self-monitoring, which may even be more efficient than laboratory monitoring,[7] has become a reality.

Yet oral anticoagulation remains a laborious and poorly predictable therapy. Recently, oral direct thrombin inhibitors were introduced. These agents do not need anticoagulant monitoring. In a large clinical trial on venous thromboprophylaxis ximelagatran showed better efficacy than low-molecular-weight heparin[8] and in the large ESTEEM study in coronary artery disease ximelagatran plus aspirin showed superiority over aspirin alone.[9] After a proper dose-finding study[10] the drug has now been tested against warfarin in patients with atrial fibrillation in two large trials: SPORTIF-III[11] and SPORTIF-V.[12]

In 3407 patients with nonvalvular atrial fibrillation, ximelagratran 36 mg twice daily in an open-label design and in 3922 patients in a double-blind set-up proved not inferior to warfarin (INR 2 to 3) in stroke prevention with similar major (*table 1*), but less minor bleeding.

Table 1. *Efficacy of the direct thrombin blocker ximelagatran in patients with atrial fibrillation*

Trial	Stroke/systemic embolism		OR (95% CI)	P value
	Ximelagatran (36 mg bid)	Warfarin (INR 2 to 3)		
SPORTIF-III[11]	40/1704 (2.3%)	56/1703 (3.3%)	0.71 (0.48-1.07)	0.10
SPORTIF-V[12]	51/1960 (2.6%)	37/1962 (1.9%)	1.38 (0.91-2.10)	0.13
Total	91/3664 (2.5%)	93/3665 (2.5%)	0.98 (0.74-1.30)	0.94

Just as in the previous trials, transient liver enzyme elevations were seen in up to 3% with 24 mg,[6] and 6 and 7% with 36 mg twice daily in the SPORTIF trials and ESTEEM,[9] respectively. Recently, the new oral direct thrombin blocker dabigatran was evaluated in a 12-week dose-finding warfarin-controlled study in 502 patients with atrial fibrillation.[13] It shows an acceptable efficacy and safety profile, but liver enzyme elevation was only seen in less than 1% of patients on dabigatran (*table 2*). These results are the basis for the very large phase III trial of dabigatran *vs* warfarin (RELY).

Not only direct thrombin inhibitors have been tested in stroke prevention in atrial fibrillation. The novel once-weekly subcutaneous factor Xa-specific pentasaccharide idroparinux was compared with warfarin in the AMADEUS study (5700 patients). Unfortunately, this trial was prematurely terminated due to increased severe bleeding in the idroparinux-treated patients. Possibly, the very long-acting pentasaccharide cannot be adequately antagonised in case of bleeding. In the near future oral factor-Xa inhibitors will become available and will surely be evaluated against warfarin in atrial fibrillation.

Beside novel anticoagulants, antiplatelet therapy has been evaluated in stroke prevention. Aspirin has also shown to be protective against stroke in atrial fibrillation with a relative risk reduction of 36% compared with placebo,[14] much less than warfarin *vs* control (62% relative risk reduction). In direct comparison with warfarin, aspirin is less effective but can be used as an excellent alternative in patients not willing or capable of using the cumbersome oral anticoagulants. Also the platelet adenosine diphosphate (ADP) receptor antagonist clopidogrel, which has a good track record in the invasive and noninvasive treatment of coronary artery disease, has been tested against warfarin in aspirin-treated patients with atrial fibrillation in the 6500 patients of the ACTIVE-W study. This trial was also stopped prematurely, this time because of lack of efficacy relative to warfarin. The other ACTIVE studies are being continued. ACTIVE-A is a randomised trial of aspirin plus clopidogrel *vs* aspirin alone in patients with atrial fibrillation not willing or capable of using oral anticoagulants. ACTIVE-I is a randomised trial of irbesartan *vs* placebo on top of other therapy in patients with atrial fibrillation participating in the other ACTIVE studies.

If new drugs become registered for atrial fibrillation, it is very likely that warfarin will be replaced by these alternatives that are much easier to use. Although the first results look promising, there are unexpected safety and efficacy problems. Safety issues include bleeding and liver toxicity. Since warfarin use is associated with a yearly risk of at least 1% major bleeding, excess haemorrhagic complications of new drugs will not be easily found. Very long-acting drugs without proper antidotes such as idroparinux should be avoided. Although, to a lesser extent, liver enzyme elevations were observed in the early studies with statins, this turned out to be a minor problem. Whether this will also be the case for newer drugs is unknown and should be further tested. If after treatment initiation frequent liver enzyme testing proves to be necessary in the first six months, this will counterbalance the new drugs potential advantages with regard to drug monitoring. Furthermore, only patients similar to those in the large trials will be eligible for the trade-in of

Table 2. *Efficacy and safety of the new oral direct thrombin blocker dabigatran in a 12-week warfarin-controlled dose-finding study in atrial fibrillation*[13]

	Dabigatran (all doses) (n=472)	Warfarin (INR 2 to 3) (n=70)	P value
Stroke and thromboembolism	0.5%	0	0.61
Major bleeding	0.9%	0	0.98
All bleeding	18%	18%	
ALT elevation >3 times ULN	0.7%	0	0.85

ALT = alanine aminotransferase; ULN = upper limit of normal.

warfarin, because safety data on the new drugs in other atrial fibrillation patients are lacking. If safety seems good in a broader patient population, the drugs may find their way into general use in atrial fibrillation. But this process will take a while, and in the meantime aspirin-controlled studies with agents such as clopidogrel, which has a more established safety profile than the new drugs, will be finished. Depending of the outcome, physicians willing to trade-in warfarin in their atrial fibrillation patients must decide on which agent they will go for.

Finally, also nonpharmacological measures have been evaluated in stroke prevention in atrial fibrillation. For a long time routine electrocardioversion was thought to be the cure for atrial fibrillation with subsequent discontinuation of antiarrhythmic drugs and oral anticoagulation. However, this strategy has not been found to be superior to the combination of just rate control and proper oral anticoagulation.[15,16] More sophisticated techniques include internal electroablation of the left atrium and occlusion of the left atrial appendage. The effect on stroke prevention of these interventions, however, remains to be established.

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REVIEW

The story of PON1: how an organophosphate-hydrolysing enzyme is becoming a player in cardiovascular medicine

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ABSTRACT

Since the discovery of human serum paraoxonase (PON1), the enzyme has been the subject of various fields of research. Initially, PON1 was identified as an enzyme capable of hydrolysing organophosphate compounds, but there is a growing body of evidence that PON1 plays a role in lipid metabolism and the onset of cardiovascular disease. Still, the precise mechanism by which PON1 functions *in vivo* remains to be clarified. Here we will briefly review developments in the field of PON1 research which merit further attention.

KEYWORDS

PON1, HDL, LDL oxidation, cardiovascular disease

A BRIEF HISTORY OF PARAOXONASE

In 1946, Abraham Mazur was the first to report the presence of an enzyme in animal tissue which was able to hydrolyse organophosphate compounds.[1] This led to the initial identification of the human serum paraoxonase (PON1) enzyme in the early 1950s.[2,3] PON1 was named after its ability to hydrolyse the organophosphate substrate paraoxon (paraoxonase activity, EC 3.1.8.1), which is the toxic metabolite of the insecticide parathion. Because PON1 could also hydrolyse aromatic esters, such as phenylacetate (arylesterase activity, EC 3.1.1.2), the term 'A-esterase' was introduced for the enzyme hydrolysing both compounds.[2,3] This led to much discussion during the following years as to whether one enzyme or two were responsible for the paraoxonase and arylesterase activity,[4] but finally, conclusive evidence was delivered that both paraoxonase activity and arylesterase activity were properties of PON1.[5] When Mackness and colleagues demonstrated that PON1 could prevent the accumulation of lipoperoxides in low-density lipoprotein (LDL),[6] thus linking PON1 to cardiovascular disease, the scientific interest in PON1 increased immensely. Despite the boom in research, to date the exact physiological function of PON1 is still unclear.

PON1 FAMILY

PON1 belongs to the family of serum paraoxonases, consisting of PON1, PON2 and PON3. The genes coding for these enzymes are all located next to each other on the long arm of chromosome 7 (7q21.3-q22.1).[7] PON1 and PON3 are expressed in the liver and excreted in the blood where they are associated with the high-density lipoprotein (HDL) particle.[8,9] PON2 is not present in blood, but is expressed widely in a number of tissues, including the liver, lungs, brain and heart.[10] Of the paraoxonase family, PON1 is the most investigated and best understood member.

Recently, the crystal structure of a recombinant PON variant was solved, making PON the first HDL-associated protein of which the three-dimensional makeup has been elucidated.[11] PON is a six-bladed β-propeller, each blade consisting of four β-sheets, and contained in the central

[**]A.F.H. Stalenhoef was not involved in the handling and review process of this paper.

tunnel of the enzyme are two calcium atoms needed for the stabilisation of the structure and the catalytic activity.[11] Three α helices, located at the top of the propeller, are involved in the anchoring to the HDL particle.[11] The clarification of the crystal structure led to more understanding of the catalytic mechanisms underlying PON1's wide substrate range. Furthermore, the crystal structure gave more information about the binding and orientation of PON1 to the HDL particle, revealing that the active site of the enzyme was directed towards the surface of the HDL particle.[11]

Since the compounds that can be hydrolysed by PON1, e.g. organophosphates (paraoxon and diazoxon), warfare agents (soman and sarin) and aromatic esters (phenyl acetate) are nonphysiological substrates,[12] these activities are not likely to be the physiological functions of PON1. Recent investigations have suggested that the hydrolytic activity towards lactones (cyclic esters) is the native activity of PON1: structure-activity studies show that lactones are PON1's preferred substrate for hydrolysis.[13] In addition, all members of the PON family have lactonase activity, implying that this activity has been conserved throughout the evolution of the enzyme.[14] *In vivo*, there is a wide inter-individual variation in PON1 concentration and activity. This variation is for a major part determined by common genetic variants (polymorphisms) in the PON1 gene. Four polymorphisms in the promoter region of the PON1 gene (–107C>T, –162A>G, –824G>A, –907G>C) have been reported to affect the expression and thus the serum concentration of the enzyme.[15-17] The –107C>T polymorphism has been the most important genetic determinant of PON1 levels.[15-17] The coding region of the PON1 gene contains two polymorphic sites: a leucine (L) to methionine (M) transition at position 55 (55L>M), and a glutamine (Q) to arginine (R) transition at position 192 (192Q>R).[18,19] Due to linkage with polymorphisms in the PON1 promoter region, the 55L>M polymorphism affects the enzyme concentration.[16] In addition, the 55L>M polymorphism is located in the N-terminal side of PON1, which plays a role in the binding of PON-1 to HDL,[20] and may thus alter the ability of PON1 to form a complex with HDL.[21] The 192Q>R polymorphism is responsible for a striking substrate specific difference in the hydrolytic activity of the enzyme.[18,19,22] Paraoxon is most efficiently hydrolysed by the 192R isoform,[18,19] and diazoxon, soman and sarin are more efficiently hydrolysed by the 192Q isoform.[22] The capacity of blood to hydrolyse paraoxon (paraoxonase activity) is often used as a marker for the PON1 enzyme activity. This enzyme activity reflects the combined effects of the 192Q>R polymorphism and the variation in concentration of the PON1 enzyme. In addition to the paraoxonase activity, the PON1 concentration can be measured directly in serum with an enzyme-linked immunosorbent assay (ELISA).[23] Otherwise, because PON1 esterase activity is not polymorphic (i.e. influenced by the 192Q>R polymorphism), the PON1 concentration can be estimated by measuring the arylesterase activity.[24]

The 192Q>R and –107C>T polymorphisms are responsible for an up to 13-fold interindividual variation in PON1 enzyme activity and concentration.[25] Lifestyle factors such as smoking and alcohol consumption also influence the PON1 *in vivo* status. Cigarette smoke inhibits PON1 activity *in vitro*,[26] and in agreement, paraoxonase activity is lower in smokers than in nonsmokers.[27-29] Furthermore, moderate consumption of beer, wine or spirits is associated with an increased serum PON1 activity.[30,31]

THE ROLE OF PON1 IN HUMANS

To date, the role of PON1 *in vivo* is unclear, but in general, PON1 is thought to attenuate the oxidation of LDL. This hypothesis was based on *in vitro* findings, showing that purified PON1 inhibited the accumulation of lipid peroxides in LDL.[6] In the arterial wall the oxidised LDL particle (oxLDL) is recognised by oxLDL specific receptors on the macrophage and taken up into the cell.[32] Since there is no negative feedback mechanism for this uptake, this process eventually leads to an overload of lipids in the macrophage, which causes the lipid laden macrophages to aggregate and form a fatty streak characteristic of atherosclerosis.[32] The oxidation of LDL is a key process in the pathophysiology of atherosclerosis and the onset of cardiovascular disease,[33] and therefore, it is not surprising that PON1 has been the subject of increasing scientific interest since its alleged role in the oxidation of LDL.

Apart from inhibition of LDL oxidation, there is evidence from animal and *in vitro* models that paraoxonase can protect the HDL particle from oxidation and preserve the integrity of HDL.[34,35] Furthermore, many epidemiological studies have found that polymorphisms in the PON1 gene, responsible for the variations in PON1 activity and concentration, also contribute to variation in plasma levels of HDL-C in different populations.[36-39] Because HDL has many athero-protective functions, such as the removal of excess cholesterol from tissues (reverse cholesterol transport) and the inhibition of inflammatory processes,[40,41] the preservation of the HDL particle may be a beneficial role of PON1.

In blood, PON1 can hydrolyse homocysteine thiolactones, a metabolite of homocysteine.[42] Homocysteine thiolactones can have an adverse effect on protein synthesis and may lead to endothelial dysfunction and vascular damage.[43] The detoxification of the homocysteine thiolactone may therefore be a cardioprotective function of PON1.

Other interesting discoveries with respect to PON1 come from the field of pharmacology. The LDL-cholesterol-lowering HMG-CoA reductase inhibitors (statins) have been found to affect PON1 activity, concentration and gene expression.[44-46] Reversely, since PON1 significantly predicted changes of HDL cholesterol during statin treatment in a number of populations,[47,48] PON1 may be an important effect modifier of the success of the statin treatment.

PON1 AND CARDIOVASCULAR DISEASE

As mentioned earlier, the finding that PON1 has properties to inhibit LDL oxidation *in vitro* implicated that PON1 could have a protective role in the onset of cardiovascular disease. However, the validity of those findings have been questioned since it could not be excluded that the protection against *in vitro* oxidation was caused by the detergent used during the preparation or a low-molecular mass compound copurified with PON1.[49] Still, the results from animal experimental work uniformly show that PON1 is a protective enzyme against atherogenesis: PON1 deficiency in mice results in increased oxidative stress in serum and macrophages,[50] and HDL isolated from PON1-deficient mice did not protect LDL from oxidation,[51] whereas HDL isolated from human PON1 transgenic mice (having two- to four-fold increased PON1 plasma levels) was more protective against LDL oxidation in a dose-dependent manner.[52] Finally, and perhaps the strongest evidence that PON1 plays a role in atherogenesis, PON1 deficient mice are more prone to develop atherosclerosis than wild-type mice, when fed a high-fat/high-cholesterol diet.[51]

In humans, however, the role of PON1 genetic variants, levels and activities and the onset of cardiovascular disease is less clear. Many epidemiological studies have reported conflicting results,[53] and a recent meta-analysis among 43 investigations studying the 55L>M, 192Q>R and –107C>T polymorphisms in relation to coronary heart disease (CHD), demonstrated no effect for the 55L>M and –107C>T polymorphisms and a slightly increased risk for carriers of the R-allele at position 192.[54] In general, however, the effects of single genetic variants to the onset of complex diseases (such as cardiovascular disease) are often too weak to be detected in studies of relatively small sample sizes.[55] It is therefore recommended to measure PON1 activity and concentration in addition to PON1 genotype.[25,56-58] So far there have been only a few studies (the majority being case-control studies) that have measured PON1 activity and concentration.[57] Furthermore, a major limitation of measuring PON1 in case-control studies is that blood is drawn after the cardiovascular event has taken place. In this way it is not possible to distinguish whether PON1 activity was the cause of the event or, conversely, a reflection of the event itself. To overcome this problem a prospective study design is needed. Up to now, only one prospective investigation on PON1 activity and concentration and CHD outcome has been published. This study showed that low serum PON1 activity toward paraoxon was an independent risk factor for coronary events in men with pre-existing CHD.[59]

CONCLUSION

Despite 60 years of research, the exact role of PON1 in the human body is still unclear. An important question which still needs to be answered is whether PON1 plays a role in the onset of cardiovascular disease. Promising research themes, such as the association with the lipid metabolism and the ability to hydrolyse homocysteine thiolactones support such an involvement and merit further investigation. Until now, however, most of our knowledge on the relationship of PON1 with cardiovascular disease is based on single gene association studies, and in general, the results of genetic association studies in complex diseases have been disappointing. Therefore, it is crucial that, before drawing definitive conclusions, the contribution of the PON1 protein rather than the genetic variants should be investigated in prospective studies.

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ORIGINAL ARTICLE

The effect of online status on the impact factors of general internal medicine journals

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ABSTRACT

Background: We sought to determine the effects of becoming available online on impact factors of general medicine journals.

Methods: Through MEDLINE with an institutional subscription, the 2004 online status of "Medicine, General and Internal" journals listed in the Institute for Scientific Information (ISI) Journal Citation Reports (JCR) was classified as full text on the Net (FUTON), abstract only, or no abstract available (NAA)/unavailable in MEDLINE. Similarly, through use of a home computer without an institutional subscription, the 2004 online status of the same journals was determined. For each journal, impact factors for 1992 to 2003 were obtained.

Results: Of the 102 "Medicine, General and Internal" journals listed in the ISI JCR, 71 (70%) existed in both pre-Internet (1992) and Internet (2003) eras. Of these 71 journals, those available as FUTON in 2004 had higher median impact factors than non-FUTON journals in 1992 ($p<0.0001$) and 2003 ($p<0.0001$). Journals that became available online, at least partially, had significant increases in median impact factors from 1992 to 2003 ($p<0.0001$ for journals that became available as FUTON and for journals that provided an abstract only). However, journals that became available as FUTON had a greater increase in median impact factor from 1992 to 2003 than other journals ($p=0.002$). Similar results were obtained using impact factor data according to journal online status through use of a home computer without an institutional subscription and for English-language journals only.

Conclusion: Becoming available online as FUTON is associated with a significant increase in journal impact factor.

KEYWORDS

Bias, impact factor, Internet, journals

INTRODUCTION

When caring for patients, teaching trainees, or conducting research, healthcare professionals can readily locate and access up-to-date literature in online journals, textbooks, and other resources. A free and easy-to-use tool for searching the scientific literature is MEDLINE, the primary subset of PubMed, produced by the United States National Library of Medicine. From any computer with Internet access, researchers can use MEDLINE to identify references from more than 4600 journals.[1,2] Journals must meet strict criteria to be included in the MEDLINE database. Indeed, those included in MEDLINE represent a small fraction of more than 126,000 science journals published worldwide.[3]

More than 75% of the references included in MEDLINE since 1975 include an English-language abstract. Some full-text articles are available for free through PubMed Central, a full-text archive. However, most full-text articles are available only for a fee or with a paid individual or institutional (e.g. medical school) subscription (e.g. publisher website or commercial entity such as Ovid or Science Direct).

With institutional access to MEDLINE, journal article information is available online as a full-text article (full text on the Net; FUTON), an abstract only, or citation information only (no abstract available; NAA). Notably, some journals are unavailable through MEDLINE. Journal article information accessed with a home computer without an institutional subscription is available online as free FUTON or as free abstract only, or no reference information may be available (i.e. the journal's website does not provide full-text articles, abstracts, or citation information).[3]

One measure of a journal's visibility and accessibility is the impact factor. The impact factor is a means of ranking journals by citation analysis; i.e. the more frequently a given journal's articles are cited, the higher the journal's impact factor.[4,5] For a given year (e.g. 2003), a journal's impact factor is calculated by dividing the total number

of published citations to articles in the journal during the previous two years (e.g. 2001-2002) by the number of source items (original research articles, review articles, etc) published by the journal during the same two years.[3,4,6,7] Every year, the Institute for Scientific Information publishes impact factors for 5000 science and technology journals.[4,8] Notably, fewer than 2000 of these journals are biomedical journals and not all of them are searchable through MEDLINE.

In this study, we sought to determine whether an association existed between becoming available online as FUTON or free FUTON and a change in impact factor (i.e. we hypothesised that becoming available online increases a journal's visibility and, hence, its impact factor).

MATERIALS AND METHODS

A retrospective longitudinal design was used. During December 2004, the Institute for Scientific Information listed 102 "Medicine, General and Internal" journals in its Journal Citation Reports. This group of journals comprised the dataset for this study. For each journal, impact factors for the years 1992 to 2003 (if available) and language (i.e. English, multiple languages (including English), or non-English) were determined. Because of the method of calculating the impact factor, the 2003 impact factors were the latest available during December 2004. The 2004 online status of these journals was determined through use of MEDLINE with an institutional subscription (FUTON, abstract only, or NAA/unavailable in MEDLINE) and through use of a home computer without an institutional subscription (free FUTON, free abstract only, or no reference information available). Finally, the year a journal became available as FUTON was determined from the cataloguing records of our institution's libraries, which include when database licenses were signed with journals and publishers. Notably, none of the journals in our study were available online before 1993. The full list of journals that we analysed is available from us on request or through the Institute for Scientific Information database.

Statistical analysis

Of the 102 "Medicine, General and Internal" journals the Institute for Scientific Information listed in its Journal Citation Reports during December 2004, 71 (70%) existed in both the pre-Internet era (1992) and the Internet era (2003). These 71 journals were classified according to their 2004 online status through MEDLINE with an institutional subscription (see above). The Kruskal-Wallis test along with the Wilcoxon rank-sum test was performed, comparing the median impact factors among these groups in both the pre-Internet and the Internet era. The changes in median impact factors among these groups from the pre-Internet era to the Internet era were also determined. The Kruskal-Wallis test along with the Wilcoxon rank-sum test was performed, comparing the median changes in impact factors from the pre-Internet era with the Internet era among these groups. The same analyses were carried out for English-language journals only. The Bonferroni correction for multiple comparisons was done as appropriate. The same analyses were also carried out for the 71 journals according to their 2004 online status without an institutional subscription (see above).

RESULTS

Of the 71 journals that existed in both the pre-Internet era (1992) and the Internet era (2003), 31 (44%) were available as FUTON in 2004 through MEDLINE with an institutional subscription, whereas 35 (49%) were available as abstract only and five (7%) were NAA/unavailable in MEDLINE. The median 1992 impact factor of the journals available as FUTON in 2004 was greater than that of journals available as abstract only or NAA/unavailable in MEDLINE (Kruskal-Wallis, $p<0.0001$). Likewise, the median 2003 impact factor of journals available as FUTON in 2004 was greater than that of the other journals (Kruskal-Wallis, $p<0.0001$). These highly statistically significant differences persisted when impact factor data were analysed for English-language journals only (*table 1*).

Next, the changes in median impact factors from the pre-Internet era (1992) to the Internet era (2003) were determined. Journals available as FUTON or abstract only in 2004 had significant increases in their median impact factors between 1992 and 2003 (*figure 1A*). Similar statistically significant results were found when impact factor data were analysed for English-language journals only (*figure 1B*). Compared with the other journals, those available as FUTON in 2004 had a greater increase in their median impact factor from 1992 to 2003 (Kruskal-Wallis, $p=0.002$). Similar statistically significant results were found when impact factor data were analysed for English-language journals only (*table 1*).

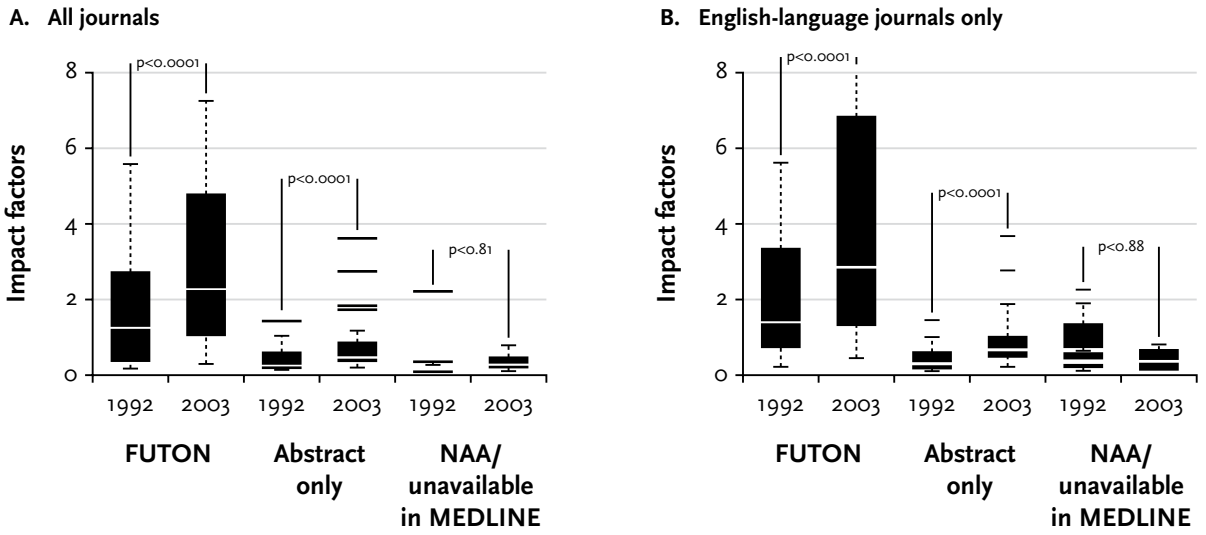
The same analyses were done using impact factor data according to online status without an institutional subscription. Of the 71 journals, 24 (34%) were available as free FUTON in 2004, 43 (60%) as free abstract only, and four (6%) had no reference information available. The median 1992 impact factor of journals available as free FUTON in 2004 was not different from that of journals available as free abstract only or those with no reference information available (Kruskal-Wallis, $p=0.67$). However, the median 2003 impact factor of journals available as free FUTON in 2004 was greater than the median impact factors of the other journals (Kruskal-Wallis, $p=0.026$). Similar statistically significant results were obtained when

Table 1. *Pre-Internet era (1992) and Internet era (2003) median impact factors of general medicine journals, according to journal online availability through MEDLINE with an institutional subscription*

Journals	No. of journals	Impact factor, median (range)		Change in impact factor from 1992 to 2003, median (range)
		Pre-Internet era (1992)	Internet era (2003)	
All journals	71			
FUTON	31	1.24 (0.16-24.46)*	2.25 (0.27-34.83)*	0.68 (-0.89-15.90)†
Abstract only	35	0.23 (0.04-1.41)	0.45 (0.19-3.61)	0.23 (-0.20-2.61)
NAA/unavailable	5	0.30 (0.07-2.21)	0.29 (0.07-0.75)	0.06 (-2.14-0.38)
Kruskal-Wallis test		p<0.0001	p<0.0001	p=0.002
English-language journals only	53			
FUTON	27	1.36 (0.17-24.46)*	2.81 (0.41-34.83)*	0.93 (-0.89-15.90)‡
Abstract only	22	0.28 (0.05-1.40)	0.62 (0.20-3.61)	0.32 (-0.13-2.61)
NAA/unavailable	4	0.31 (0.07-2.21)	0.30 (0.07-0.75)	0.14 (-2.14-0.38)
Kruskal-Wallis test		p<0.0001	p<0.0001	p=0.006

FUTON = full text on the Net (i.e. online); NAA = no abstract available. *Wilcoxon rank-sum test: FUTON *vs* abstract only, p<0.0001 (Bonferroni: significant). †Wilcoxon rank-sum test: FUTON *vs* abstract only, p=0.0023 (Bonferroni: not significant). ‡Wilcoxon rank-sum test: FUTON *vs* abstract only, p=0.0098 (Bonferroni: not significant).

Figure 1. *Pre-Internet era (1992) and Internet era (2003) median impact factors of general medicine journals, according to journal online availability through MEDLINE with an institutional subscription*



FUTON = full text on the Net; NAA = no abstract available. The white lines indicate medians; the bottom and top edges of the boxes indicate the 25th and 75th percentiles; the whiskers (marked with brackets) indicate 1.5 times the interquartile range if outliers are present; and the horizontal black lines indicate outliers.

impact factor data were analysed for English-language journals only (*table 2*).

Journals available as free FUTON and free abstract only in 2004 had significant increases in their median impact factors between 1992 and 2003 (*figure 2A*). Similar statistically significant results were found for English-language journals only (*figure 2B*). Compared with the other journals, those available as free FUTON in 2004 had a greater increase in their median impact factor from 1992 to 2003 (Kruskal-Wallis, p=0.007). Similar statistically significant differences were found when impact factor data were analysed for English-language journals only (*table 2*).

DISCUSSION

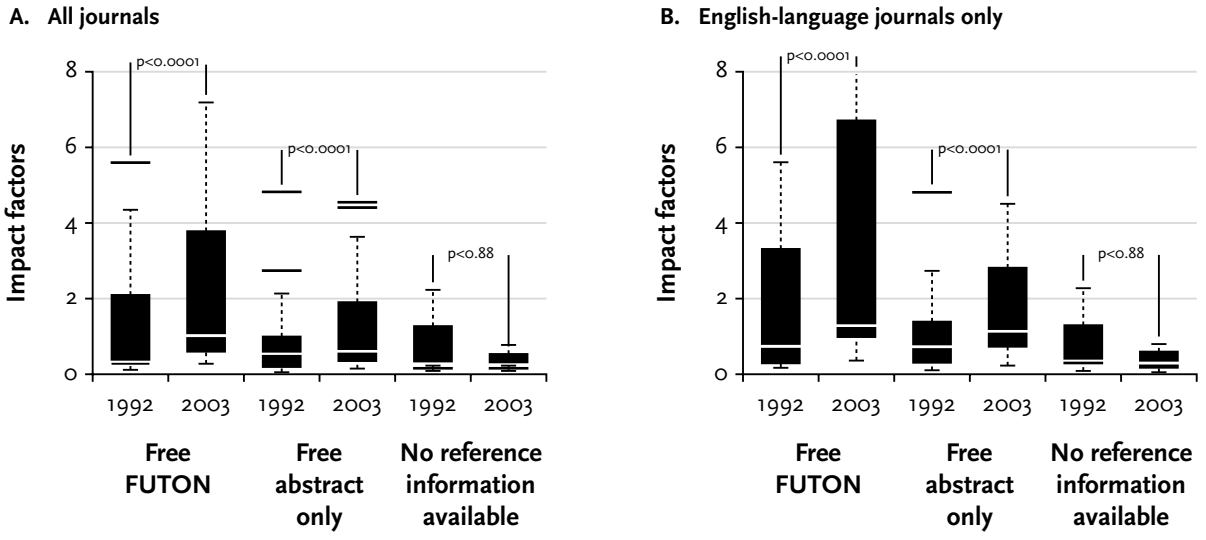
The impact factor is a means of ranking journals by citation analysis; i.e. the more frequently a given journal's articles are cited, the higher the journal's impact factor.[4,5]

Table 2. *Pre-Internet era (1992) and Internet era (2003) median impact factors of general medicine journals, according to journal online availability through use of a home computer without an institutional subscription*

Journals	No. of journals	Impact factor, median (range)		Change in impact factor from 1992 to 2003, median (range)
		Pre-Internet era (1992)	Internet era (2003)	
All journals	71			
Free FUTON	24	0.32 (0.05-24.46)*	1.02 (0.27-34.83)†	0.63 (0.04-15.90)‡
Free abstract only	43	0.56 (0.04-15.94)	0.62 (0.19-18.32)	0.22 (-0.89-9.24)
No reference information available	4	0.27 (0.07-2.21)	0.27 (0.07-0.75)	0.16 (-2.14-0.38)
Kruskal-Wallis test		p=0.67	p=0.026	p=0.007
English-language journals	53			
Free FUTON	19	0.72 (0.15-24.46)§	1.26 (0.31-34.83)‖	0.70 (0.14-15.90)¶
Free abstract only	30	0.73 (0.05-15.94)	1.12 (0.20-18.32)	0.39 (-0.89-9.24)
No reference information available	4	0.27 (0.07-2.21)	0.27 (0.07-0.75)	0.16 (-2.14-0.38)
Kruskal-Wallis test		p=0.44	p=0.013	p=0.014

FUTON = full text on the Net. *Wilcoxon rank-sum test: free FUTON *vs* free abstract only, p=0.53 (Bonferroni: not significant). †Wilcoxon rank-sum test: free FUTON *vs* free abstract only, p=0.73 (Bonferroni: not significant). ‡Wilcoxon rank-sum test: free FUTON *vs* free abstract only, p=0.005 (Bonferroni: not significant). §Wilcoxon rank-sum test: free FUTON *vs* free abstract only, p=0.47 (Bonferroni: not significant). ‖Wilcoxon rank-sum test: free FUTON *vs* free abstract only, p=0.14 (Bonferroni: not significant). ¶Wilcoxon rank-sum test: free FUTON *vs* free abstract only, p=0.02 (Bonferroni: not significant).

Figure 2. *Pre-Internet era (1992) and Internet era (2003) median impact factors of general medicine journals, according to journal online availability through use of a home computer without an institutional subscription*



FUTON = full text on the Net. The white lines indicate medians; the bottom and top edges of the boxes indicate the 25th and 75th percentiles; the whiskers (marked with brackets) indicate 1.5 times the interquartile range if outliers are present; and the horizontal black lines indicate outliers.

The size of a journal's impact factor depends on the journal's visibility and accessibility, which, in turn, may be enhanced by becoming available online. In fact, Murali *et al*. found that cardiology, nephrology, and rheumatology journals available as FUTON through MEDLINE with an institutional subscription had higher impact factors than journals available as abstract only or NAA/unavailable in MEDLINE.[3] We found similar results for 71 "Medicine, General and Internal" journals the Institute for Scientific Information listed in its Journal Citation Reports not only through use of MEDLINE with an institutional subscription but also through use of a home computer without an institutional subscription.

More importantly, however, our results suggest that a *causal* association exists between becoming available online as FUTON or free FUTON and an increase in journal

impact factor. Journals available as FUTON or free FUTON in 2004 had greater increases in their median impact factors between the pre-Internet (1992) and Internet (2003) eras than non-FUTON and non-free-FUTON journals. Similar results were obtained when impact factor data were analysed for English-language journals only. These results suggest that providing content online increases the visibility of a journal and, as a result, its impact factor.

Evidence for causality is most convincing when it is derived from an experimental study. However, data from observational studies such as ours (which had a retrospective longitudinal design) may be used to assess for causality by using criteria formulated by Hill.[9] When these criteria are applied to our study, our results suggest a causal association between becoming available online and an increase in journal impact factor as follows:

- becoming available online (e.g. FUTON or free FUTON) preceded the increase in journal impact factors;
- the association is plausible (easier access to—hence, greater likelihood to cite—journal articles available online than to articles available only in print);
- our results are consistent with those of similar studies;[3,7,10]
- the association is statistically significant;
- journals that became available online as FUTON or free FUTON had greater increases in impact factors than journals available as abstract only or free abstract only, respectively, whereas journals that did not provide content online had no increase in impact factor (suggesting a dose-response effect, where 'dose' is the amount of content made available online and 'response' is the impact factor).

Regarding the dose-response effect, we cannot determine from our study results whether a levelling of impact factors over time will occur as more journals become available as FUTON or free FUTON. In addition, we could not determine whether becoming unavailable online was associated with a decrease in impact factor.

Several confounding factors may have affected our results. For example, our data suggest that a difference exists between journals available as FUTON with an institutional subscription and journals available as free FUTON without an institutional subscription. FUTON journals had a higher median impact factor than the non-FUTON journals in both the pre-Internet and the Internet eras, whereas the free-FUTON journals had a higher median impact factor than non-free-FUTON journals in the Internet era only. The reasons for this difference are unclear. It may be due, in part, to FUTON journals enjoying greater wealth, prestige, and wider circulation in the pre-Internet era (when journals were circulated in print only) and recognising the importance of, having the capacity to commit the resources to, and supporting and marketing online access. In other words, although impact factor is associated with online availability, online availability may be a surrogate marker of journal financial wherewithal. However, our results also suggest that less resource-rich journals recognised the benefits of becoming available online. We found that the 1992 median impact factor of journals available as free FUTON in 2004 was no different from that of the non-free-FUTON journals. By 2003, however, free FUTON journals had a significant increase in their median impact factor, which, in turn, was a greater increase than for the non-free-FUTON journals. Furthermore, making some content available online (e.g. an abstract) was associated with a significant increase in impact factor between the pre-Internet and Internet eras. Journals that were NAA/unavailable in 2004 through MEDLINE with an institutional subscription or that provided no reference information through use of a home computer without a subscription had no change in their median impact factors between the pre-Internet and Internet eras. Finally, a recent study of the relationship between online hit counts on a journal website and subsequent citations found that hit counts for an article during the week after online publication predicted the number of citations of that article in subsequent years.[10] The results of this study complement ours and add to a growing body of evidence that visibility and accessibility of a journal may be enhanced by becoming available online.

Other confounding factors may have affected our results. For example, journals included in the Institute for Scientific Information Journal Citation Reports (i.e. those with impact factors) represent a select group of journals of substantial quality. Hence, the journal impact factor data that we examined may not accurately reflect the association between online status and impact factors of all "Medicine, General and Internal" journals. Indeed, in recent decades, there has been a linear growth (approximately 3.5% per year) in the number of new journal titles, and the number of articles and pages published has increased substantially.[11,12] Furthermore, 30% of the "Medicine, General and Internal" journals the Institute for Scientific Information listed in its 2004 Journal Citation Reports either did not exist or did not have impact factors from the pre-Internet era. If anything, however, these developments would likely dilute the impact factors of journals that are currently highly visible (i.e. by providing many more easily accessible references to cite). Another confounding factor may be changes in journal publication policy. Journals may inflate their impact factors by publishing more articles that are likely to generate citations (e.g. review articles) and nonsource items (e.g. editorials and letters) that are later cited.[13-15] However, it is unlikely that such policies are practiced only by journals available as FUTON or free FUTON.

The results of our study also suggest that FUTON bias exists (i.e. scholars may be more inclined to read and therefore cite easily accessible articles in journals available as FUTON and ignore relevant references that are not available as FUTON).[16] Ignoring relevant articles simply because the full-text article or its abstract is unavailable online is akin to other forms of bias such as publication bias.[16,17] Researchers and others should be aware of FUTON bias because it may affect the results and conclusions of their scholarship.

Becoming available as FUTON (or free FUTON), however, may be prohibitively costly for some journals. Many journals rely on income from journal subscriptions and advertising and may avoid becoming available as FUTON because of lost income. Some journals, previously available as free FUTON, are now available as FUTON only through subscription.[18] Success in selling online subscriptions (and advertisements on journal websites) is important for maintaining not only journal visibility but also viability.

Notably, many scholars and institutions, especially in Third World countries, cannot afford subscriptions for paper journals or online access to journals (although some journals make their online content available free of charge to scholars in Third World countries).[19,20] Indeed, our institution's libraries pay nearly US $1 million annually for access to approximately 2800 journals available as FUTON. This situation has prompted some to suggest new means of publishing the results of research and other forms of scholarship without relying on traditional journals[21] or to create free access to online journals by researchers and scholars in Third World countries.[19] In fact, government agencies, publishers, and other organisations are discussing how to develop more open access to research literature.[22,23]

CONCLUSION

Journals that are available as FUTON or free FUTON are more visible and therefore have higher impact factors. Furthermore, becoming available online as FUTON or free FUTON may be causally associated with a significant increase in journal impact factor. These findings also suggest that FUTON bias exists (i.e. ignoring a relevant article simply because it is unavailable online). Researchers and others should be aware that these forms of bias might affect the results and conclusions of their scholarship.

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ORIGINAL ARTICLE

Gastrointestinal disorders and symptoms: does body mass index matter?

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ABSTRACT

Background: Recent studies have shown inconsistent results about the association between body mass index (BMI) and gastrointestinal disorders. The aim of this study was to assess the association between BMI and gastrointestinal disorders in patients referred for endoscopy.

Methods: Consecutive patients received a questionnaire about gastrointestinal symptoms prior to upper gastrointestinal endoscopy. The association between BMI and gastrointestinal disease and related symptoms was determined by adjusted logistic regression analyses.

Results: A total of 1023 subjects were included, 303 (35%) subjects were overweight (BMI 25 to 30 kg/m^2), an additional 118 (14%) subjects were obese (BMI >30 kg/m^2). Overall, 42% of the patients experienced symptoms of gastro-oesophageal reflux disease (GERD), 70% dyspepsia and 55% lower abdominal symptoms. In obese patients the prevalence of GERD was higher (52%) compared with normal weight (44%) and overweight (44%) (ns). Reflux oesophagitis was found in 13, 17 and 19% for normal weight, overweight and obese, hiatus hernia in 7, 9 and 11% and Barrett's oesophagus in 6, 7 and 8%, respectively.

Conclusion: More than half the patients undergoing upper gastrointestinal (GI) endoscopy were overweight or obese. In this patient population, no relation between BMI and GI disorders and symptoms was found. However, a small but statistically insignificant trend was observed toward obesity for patients with GERD-associated symptoms.

KEYWORDS

Body mass index, endoscopy, gastrointestinal disorders, gastrointestinal symptoms

INTRODUCTION

The prevalence of obesity is increasing worldwide. In the past 20 years, the prevalence of obesity has doubled to 12% in the Netherlands and has become a major threat to public and clinical health.[1,2] Obesity is clearly acknowledged as a risk factor for several chronic diseases, such as diabetes mellitus type 2 and cardiovascular diseases. Moreover, obesity has recently been associated with several forms of gastrointestinal cancer, such as colon cancer, oesophageal adenocarcinoma and gallbladder disease.[3-9]

A potential role of obesity in gastrointestinal symptoms is unclear. Reports from several health surveys show inconsistent results. Most recent studies show a relationship between obesity and the occurrence of gastrointestinal symptoms, especially of heartburn and regurgitation.[10-16] This relation might be explained by the fact that obese persons experience a higher intra-abdominal pressure, slower oesophageal transit and decreased acid clearance from the oesophagus due to hiatus hernia than persons with a normal body mass index (BMI).[17-19] Consequently, hiatus hernia can cause GERD symptoms. Additionally, data from two large studies show that dyspeptic symptoms decline if overweight patients lose weight.[20,21]

Besides upper gastrointestinal symptoms, data are also scarce on a possible relation between obesity and upper gastrointestinal pathology.[22] The patient population referred for upper gastrointestinal endoscopy is prone to organic diseases due to long-term persistent symptoms not reacting to acid inhibitors. The results of the present study, in a patient population referred for upper gastrointestinal endoscopy, could reveal new insights into the relation between patients BMI and gastrointestinal symptoms and disease. The outcome may help in differentiating between gastrointestinal diseases based on body mass index and gastrointestinal symptoms.

METHODS

Subjects

A total of 1103 consecutive patients consented to participate in this study. They were all referred to two experienced gastroenterologists at the Canisius Wilhelmina Municipal Hospital, Nijmegen, the Netherlands, by general practitioners or specialists for diagnostic upper gastrointestinal endoscopy between March 2002 and March 2004. All included patients were 18 years or older.

Two weeks prior to endoscopy, the patients received a questionnaire that included demographic information, body weight and height, history of smoking, amount of alcohol and coffee intake, medical history and present use of medication. We excluded patients with a history of gastrointestinal disease, such as cancer, inflammatory bowel disease, celiac disease and gastrointestinal resections. Patients who did not complete the questionnaire were excluded as well.

Definitions

BMI was calculated as body weight (kg) divided by the square of height (m) and categorised according to the World Health Organisation (WHO) classification of overweight and obesity: normal weight BMI <25 kg/m^2, overweight BMI 25 to 30 kg/m^2, obesity BMI ≥30 kg/m^2.[1] Acid inhibitors were defined as antacids, H_2-receptor antagonists and proton pump inhibitors. Coffee and alcohol intake were divided into user or non-user and smoking into current smoker or non-smoker/ex-smoker.

Patients were asked to score gastrointestinal symptoms over the past four weeks by a validated gastrointestinal symptom rating scale (GSRS).[23] This included specific questions about the type of symptoms and severity on a seven-point Likert scale. Symptoms were categorised into three groups: 'GERD' (gastro-oesophageal reflux disease), 'dyspepsia' and 'lower abdominal'. 'GERD' was defined as heartburn and regurgitation. Epigastric pain, abdominal bloating and nausea were categorised as 'dyspepsia'. 'Lower abdominal' comprised pain in the lower abdomen (general, after a meal, when hungry, after defecation, diarrhoea and constipation). Severity of gastrointestinal symptoms was described as no symptoms, mild, moderate, quite a lot, severe, very severe and unbearable symptoms. None and mild symptoms were combined as 'no symptoms' and compared with the others.

All gastric and duodenal diagnosis found at endoscopy were confirmed by pathology reports. Barrett's oesophagus was defined by endoscopic 'Barrett's oesophagus' or 'metaplasia' in the pathology report. In this way, gastritis and duodenitis diagnosed by endoscopy were confirmed by pathology reports. Also, endoscopic 'suspicious for oesophagus or gastric malignancies' were confirmed to pathologically proven malignancies. Active *Helicobacter pylori* infection was proven by histological investigations of antral biopsy specimens.

Statistical analysis

Primary analysis investigated the association between BMI and the prevalence of gastrointestinal symptoms. In addition, we assessed whether overweight and obese patients differ in gastrointestinal pathology compared with the group with normal weight. For this purpose, we initially studied the three BMI groups for basic demographics and use of nonsteriodal anti-inflammatory drugs (NSAIDs) or acid inhibitors.

Also the frequencies of the (categorised) gastrointestinal symptoms in the study population were assessed. The relations between BMI and both gastrointestinal symptoms and diseases were analysed using Pearson χ^2 test. The evaluation of BMI as a risk factor for gastrointestinal symptoms and disease was determined by adjusted logistic regression. Factors used for adjustment (age, gender, *Helicobacter pylori* infection, alcohol and coffee consumption, current smoking and use of NSAIDs or acid suppressive medication) were made explicit by literature. An additional analysis was performed to assess whether BMI influences the relation between hiatus hernia and GERD symptoms. Analyses were performed using SAS statistical software, version 8.0.

Results

A total of 1103 patients were included in this study. We excluded four patients because they were younger than 18 years, 33 patients who had a history of gastrointestinal cancer, 14 patients with a history of chronic gastrointestinal disease and 29 patients with a gastrointestinal resection in the past. In total, 1023 patients were eligible for analysis in this study, 49% were male and the mean age of the population was 55.4 years (SD 15.4). Mean BMI was 25.5 (SD 4.5) kg/m^2. Half of the patient population was overweight (35%) or obese (14%) (*table 1*). Statistically significantly more women were obese (p<0.01). In the study population, prevalence of acid suppressive medication was high as expected (total of 5.5% were taking H_2-receptor antagonists, and 47.6% were on proton pump inhibitors), but not different between normal weight (53%), overweight (58%) and obese (51%) patients (p=0.50).

In the previous four weeks, GERD symptoms were reported by 45%, dyspepsia by 67% and lower abdominal symptoms by 59% of the total study population. These percentages did not differ significantly between the three BMI groups (*table 2*). Half of the patients in the obese group (52%) experienced a GERD symptom in the four weeks prior to upper gastrointestinal endoscopy compared with 44% in both normal and overweight groups. This finding was largely contributable to heartburn, but even this difference was not found to be statistically significant.

Table 1. *Demographics and body mass index*

Demographics (%)	Body mass index (kg/m²)			P value
	<25 (n=437)	25-30 (n=303)	≥30 (n=118)	
Mean age (SD)	53.5 (16)	57.5 (15)	54.4 (14)	0.78
Older than 50	268 (61%)	218 (72%)	79 (67%)	<0.05
Male gender	209 (48%)	171 (56%)	44 (37%)	<0.01
Western European origin	356 (91%)	267 (95%)	97 (91%)	0.09
Current alcohol users	221 (51%)	199 (66%)	56 (48%)	<0.01
Coffee users	372 (86%)	268 (90%)	100 (87%)	0.27
Current smoker	157 (36%)	77 (25%)	30 (25%)	<0.01
NSAID use	7 (3%)	3 (2%)	5 (7%)	0.12
Antacids	2 (1%)	2 (1%)	0 (0.0%)	0.67
H_2-receptor antagonists	17 (6%)	9 (5%)	4 (5%)	0.79
Proton pump inhibitors	120 (46%)	85 (51%)	35 (46%)	0.89

Table 2. *Gastrointestinal symptoms and body mass index*

Symptoms (%)	Body mass index (kg/m²)			P value*
	<25	25-30	≥30	
GERD	194 (44%)	134 (44%)	61 (52%)	0.33
Heartburn	138 (33%)	101 (35%)	51 (44%)	0.07
Regurgitation	157 (38 %)	116 (41%)	49 (44%)	0.49
Dyspepsia	299 (68%)	198 (65%)	83 (70%)	0.54
Lower abdominal	268 (61%)	173 (57%)	67 (57%)	0.44

*Adjusted for gender, age, origin, smoking, use of alcohol, coffee, gastric acid suppressive medication and NSAIDs, infection with *Helicobacter pylori*. GERD = gastro-oesophageal reflux disease.

Table 3. *Body mass index and gastrointestinal disease*

Gastrointestinal disease	Body mass index (kg/m²)			P value*
	<25	25-30	≥30	
Normal	219 (50%)	148 (49%)	57 (48%)	0.91
Oesophagitis	56 (13%)	50 (17%)	23 (19%)	0.13
Gastritis	85 (20%	44 (15%)	24 (21%)	0.16
Duodenitis	23 (5%)	12 (4%)	5 (4%)	0.68
Peptic ulcer	18 (4%)	10 (3%)	6 (5%)	0.68
Hiatus hernia	29 (7%)	27 (9%)	13 (11%)	0.24
Barrett's oesophagus	27 (6%)	20 (7%)	10 (8%)	0.67
Oesophagus carcinoma	3 (1%)	0 (0%)	0 (0%)	0.23
Gastric carcinoma	0 (0%)	1 (0.3%)	0 (0%)	0.40
Helicobacter pylori infection	60 (14%)	34 (11%)	17 (14%)	0.53

*Adjusted for gender, age, origin, smoking, use of alcohol, coffee, acid inhibitors and NSAIDs, infection with *Helicobacter pylori*.

Table 4. *Association between hiatus hernia and GERD symptoms*

BMI*	Hiatus hernia	GERD (%)	P value
Normal (<25 kg/m²)	Yes	18 (62.1%)	0.05
	No	174 (43.1%)	
Overweight (25-30 kg/m²)	Yes	17 (63.0%)	0.04
	No	116 (42.2%)	
Obese (≥30 kg/m²)	Yes	7 (53.9%)	0.84
	No	53 (51.0%)	

*Trend over BMI subgroups, p=0.55. GERD = gastro-oesophageal reflux disease.

In approximately half of the population, endoscopy did not reveal any abnormalities (*table 3*). Regarding gastrointestinal pathology, no differences were found between the three BMI groups. A small but insignificant trend could be observed for oesophageal diseases. For the normal weight, overweight and obese patients we found oesophagitis in 13, 17 and 19%, hiatus hernia in 7, 9 and 11% and Barrett's oesophagus in 6, 7 and 8%, respectively.
Table 4 describes the association between hiatus hernia and GERD symptoms, subdivided for the BMI classes. The normal and overweight patients with hiatus hernia are more prone to GERD symptoms, in obese patients this association was not present.

DISCUSSION

We studied the association between BMI and prevalence of gastrointestinal symptoms and upper gastrointestinal abnormalities in patients referred for endoscopy. Half of our population was overweight or obese and again in half endoscopy did not reveal any abnormalities. With an increase in BMI, there was a small but not statistically significant increase in prevalence of diseases and symptoms related to the oesophagus.
Obesity is becoming more and more prevalent. Obese patients are not only at risk for cardiovascular diseases and diabetes mellitus, but also have a decreased health-related quality of life.[24,25] Medical consumption of this specific population is higher and in the near future the health system will need investments to cover this.
The association between BMI and upper gastrointestinal diseases has been studied before. The population-based study by Locke *et al*. aimed at assessing risk factors for reflux oesophagitis.[12] Patients defined as obese conform the WHO guidelines (>30 kg/m^2) had a three times higher risk of oesophagitis (OR 2.8, 95% CI 1.7 to 4.5). In our study we did find a small trend for the association between obesity and oesophagitis, but not as firm as Locke and colleagues. We did, however, find not only reflux oesophagitis but also other oesophagus-related diseases (Barrett's oesophagus and hiatus hernia) to be slightly more prevalent in the higher BMI classes. A recent study by El-Serag *et al*. also showed more frequent hiatus hernia and reflux oesophagitis among the overweight and obese.[10] They suggested that obesity could be the cause of hiatus hernia, which could be followed by GERD and reflux oesophagitis. Hiatus hernia was also related to GERD symptoms in our study, but not in the obese patients, which implicates involvement of other factors than body mass index for the occurrence of hiatus hernia.
The literature is inconsistent about the association between BMI and gastrointestinal symptoms. This inconsistency could be explained by several factors: the choices for certain cut-offs, the study population and the absence of the association. Study protocols found in literature used different cut-off points for BMI, some were based on statistical reasons (e.g. quartiles), others adopted cut-offs from other publications. For better comparison we used the most common definition, described by the WHO.[1] In contrast to our study the association was previously studied in the general population and in outpatients, whereas we studied patients referred for upper gastrointestinal endoscopy, which is a population with a higher occurrence of upper gastrointestinal diseases and related symptoms. Moreover, in our population both symptoms and diagnosis could be studied.

The large community-based randomised controlled trial by Murray *et al*. in the United Kingdom showed a positive correlation between BMI and prevalence of gastrointestinal symptoms.[11] In their study, 21% of the patients were obese and 41% overweight according to WHO guidelines, which is quite similar to our results with 14 and 35% obese and overweight patients, respectively. Their results showed adjusted odds ratios for frequency of symptoms occurring at least once a week in overweight patients compared with those of normal weight of 1.8 (95% CI 1.33-2.50) for heartburn and 1.5 (95% CI 1.13-1.99) for regurgitation. Corresponding odds ratios relating to obese patients were 2.9 (95% CI 2.07 to 4.08) and 2.2 (95% CI 1.44 to 3.45), respectively. This British study was conducted in the general population, while we studied the association between BMI and GERD symptoms in a population referred for upper gastrointestinal endoscopy.
All studies have their limitations. In our study, body weight and height were obtained on a self-report form, rather than measured by a physician. Especially obese patients are more likely to underreport their body weight, which may have lead to an underestimation of our obese population. It is unclear whether underreporting of body weight plays an important role in gastrointestinal patients. These patients may be well aware of their body weight, as it is usually measured during their visits to the gastroenterologist. Moreover, the majority of our study population were taking or had been taking acid suppressive medication, which might contribute to the lower prevalence of peptic ulcer disease and reflux oesophagitis, compared with other study results handling the relation between BMI and reflux oesophagitis. However, our patient population was a better reflection of common practice, where many patients had already experienced pretreatment with any acid suppressive medicament.
The observational setting of this study introduces physician behaviour as confounding. All patients in our study were referred by their general practitioner. Patients with a higher BMI can be referred to secondary care at an earlier stage than others, because of the referring doctor's knowledge of the current literature. This confounding-by-indication could have interfered with our results, but more

importantly, it introduces a poor comparison with other (endoscopic) study results.

In conclusion, more than half of the patients undergoing endoscopy were overweight or obese. In this patient population, no relation between BMI and GI disorders and symptoms was found, although a small but statistically insignificant trend was observed toward obesity for patients with GERD associated symptoms.

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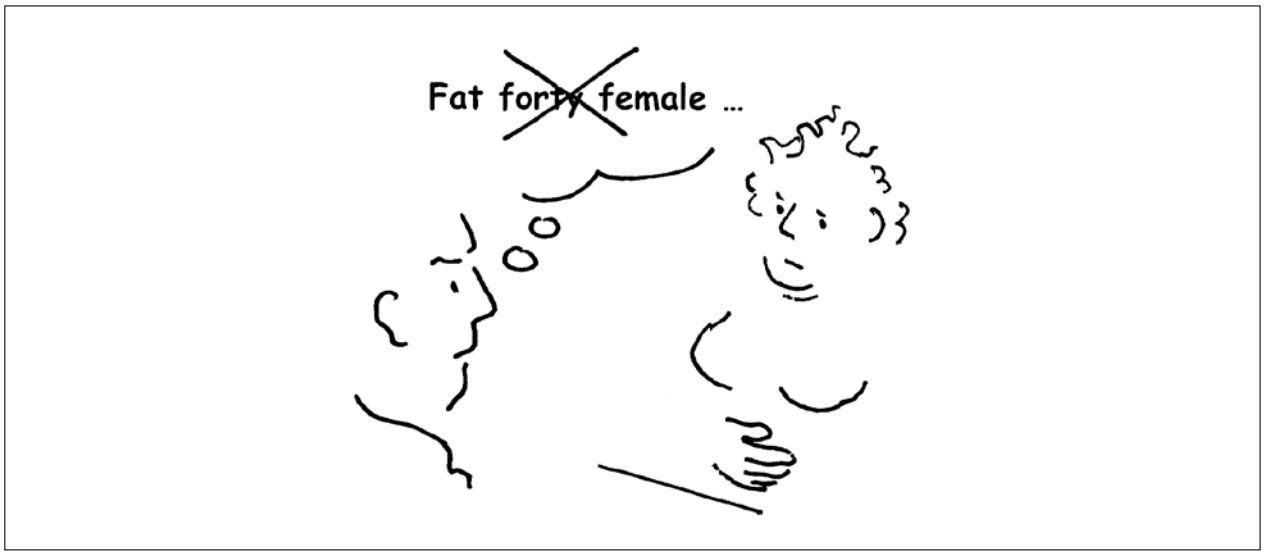

Van Oijen, et al. Obesity and gastrointestinal disorders.

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CASE REPORT

Monoclonal gammopathy in human leishmaniasis

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ABSTRACT

A 64-year-old female with IgGk monoclonal components (total 45 g/l) and 30% abnormal plasma cells and plasmoblasts in bone marrow is reported. After the identification of leishmania in the bone marrow, liposomal amphotericin B was used and a progressive resolution of the gammopathy was documented.

KEYWORDS

Monoclonal gammopathy, visceral leishmaniasis

INTRODUCTION

Visceral leishmaniasis, a parasitic disease, is usually considered a typical infantile syndrome with a high incidence in southern Italy; however, the occurrence of the disease has recently been observed in immunocompetent adults as well. The detection of monoclonal components is exceptional in patients with visceral leishmaniasis.[1,2] In contrast, monoclonal alterations of immunoglobulins are common in canine leishmaniasis.[3]

CASE REPORT

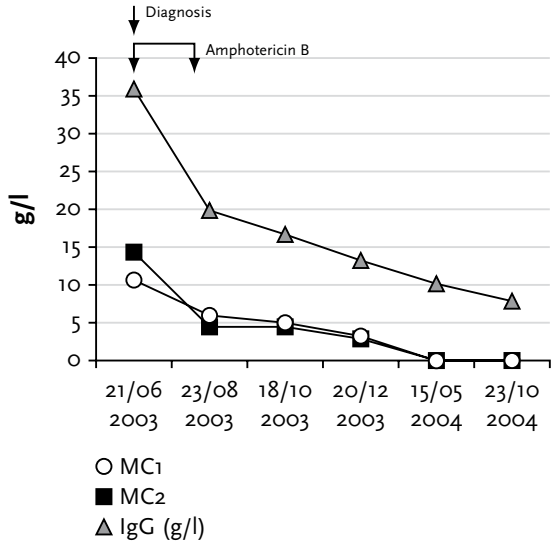
We report a case of visceral leishmaniasis and monoclonal components observed in our department during the spring of 2003.

A 64-year-old woman with a history of intermittent fever (over 38°C) and headache within the last eight months was admitted in our department. She was complaining of general discomfort, fatigue, loss of appetite and recent weight loss (about 2 kg in two weeks). Her personal history was not significant, the only relevant data being trips to Morocco (2000), Egypt (2001) and Russia (2002) and a holiday in south-eastern Italy ten months previously. Physical examination failed to demonstrate enlarged lymph nodes, but liver and spleen were palpable. The laboratory data showed mild normochromic normocytic anaemia (haemoglobin 6.6 mmol/l, MCV 89 fl), mild thrombocytopenia (130 x 10^9/l), slightly decreased white blood cell count (total 3.9 x 10^9/l neutrophils 47% lymphocytes 40%, monocytes 8% and eosinophils 5%), a relevant increase in ESR (102 mm/h) and CRP (108.5 mg/l). The total proteins were very high (107 g) and protein electrophoresis showed an increase in gammaglobulins (45 g/l) with 2 IgGk monoclonal components. The Bence-Jones protein was undetectable, while β_2-microglobulin was higher than normal (3955 mg/l). A multiple myeloma was considered[4] and a bone marrow aspirate together with bone marrow biopsy performed. Abnormal plasma cells and plasmoblasts representing more than 30% of all marrow cells were observed confirming the clinical hypothesis. However, the presence of parasites was documented.[5] The definitive diagnosis was reached by a positive *Leishmania infantum* serological test (immunofluorescent antibody test). The patient was treated with liposomal amphotericin B for three weeks (total dose 1225 mg) with a prompt resolution of symptoms; the hepatosplenomegaly disappeared within five months. An initial decrease in monoclonal IgGk was observed, but a completely normal level was only achieved after 12 months. The recovery of normal blood parameters was observed at the same time (*figure 1*).

DISCUSSION

Previous case reports indicate that visceral leishmaniasis can be misdiagnosed as myeloma,[1,2] mixed cryoglobulinaemia[6] and malignant lymphoma,[7] so great attention

Figure 1. *Immunoglobulin (IgG) total dosage and single monoclonal component (CM) concentration at diagnosis and during the follow-up*



The monoclonal components disappeared 11 months after diagnosis and 9 months after the end of treatment with amphotericin B.

needs to be paid to patients who have travelled in a risk area and who develop a rapid increase in paraproteins. In our case, the travel in southern Italy in a three week to 18 month period before the symptoms developed should suggest a parasitic origin of the disease. It is important to underline that the extremely long duration of the monoclonal IgG component in our patient, even after a complete recovery of the symptoms and disappearance of positive serological data, may also occur in some patients with unrecognised leishmaniasis which resolves spontaneously.[8] The annual incidence of visceral leishmaniasis in Italy is considered to be about 30 to 50 cases, but is probably greatly underestimated.[9] Therefore, it is important to be aware that acute development of monoclonal paraproteins may be related to a parasitic infection rather than a myeloma.

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Netherlands
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CASE REPORT

Isotretinoin-induced inflammatory bowel disease

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ABSTRACT

Three case reports on inflammatory bowel disease associated with use of isotretinoin are described. All three patients were male adolescents, in good health when starting isotretinoin (for acne treatment for about six months). Several weeks after discontinuation of isotretinoin the patients developed severe symptoms requiring hospitalisation. The diagnosis of ulcerative colitis was made in two of these patients, while in the third patient Crohn's disease was diagnosed.

Although inflammatory bowel disease is described as an adverse drug reaction in the product information of isotretinoin, few cases have been described so far. The link with prior isotretinoin use may not be recognised by the patient or the physician, since the diagnosis of inflammatory bowel disease is often preceded by several years of vague symptoms. On the other hand, spontaneous onset of inflammatory bowel disease (not related to isotretinoin) cannot be excluded. We appeal to the readers for a reaction to this, to shed more light on the likeliness of this alleged association.

KEYWORDS

Adverse drug reaction, Crohn's disease, IBD, isotretinoin, ulcerative colitis

INTRODUCTION

Isotretinoin (Roaccutane®) was approved for marketing in the Netherlands in 1984. It is used for the treatment of severe forms of acne, resistant to adequate standard therapy with systemic antibiotics and topical treatment. Isotretinoin affects the acned skin by decreasing sebum production and normalising increased skin shedding.[1] In the product information of isotretinoin it is stated that gastrointestinal adverse drug reactions occur with a chance of less than 1/10,000. Furthermore, in the section 'special warnings and precautions for use' inflammatory bowel disease has been associated with isotretinoin therapy in patients without a prior history of intestinal disorders.[1] Although inflammatory bowel disease (IBD) is described as a possible adverse drug reaction in the product information of isotretinoin, this association has been given little attention in the literature. We present three case reports on this association, and invite specialists to comment on this alleged relationship.

MATERIAL AND METHODS

The Netherlands Pharmacovigilance Centre Lareb maintains the spontaneous adverse drug reaction reporting system in the Netherlands on behalf of the Dutch Medicines Evaluation Board. Physicians and pharmacists have been reporting adverse drug reactions (ADRs) to Lareb since 1985. Patients may report ADRs since April 2003. Lareb reports are sent to the European Medicines Agency (EMEA), and are included in the worldwide database of the World Health Organisation (WHO).

RESULTS

In the period between 1985 and August 2005 the Netherlands Pharmacovigilance Centre Lareb received three reports of inflammatory bowel disease associated with the use of isotretinoin.

Case report 1

The first report came from a 19-year-old male patient who gave Lareb permission to contact his gastroenterologist for additional information. The patient had taken isotretinoin for acne vulgaris, 20 mg three times daily, for a period of five and a half months. He was not on any other medications. There were no intestinal disorders in either his own medical history or that of his family. Seven months after starting isotretinoin, thus one and a half month after discontinuation of isotretinoin, he developed bloody diarrhoea, dehydration and severe weight loss. He was hospitalised after losing 10 kg weight within two weeks. An infectious cause of diarrhoea was excluded by faeces cultures and parasitology. Colonoscopy revealed ulcerative (pan)colitis. This was confirmed by histology which showed ulcerative colitis with crypt abscess and cryptitis. Ultrasound examination of the abdomen showed no involvement of the small intestine, making Crohn's disease unlikely. The patient was treated with intravenous prednisone, mesalazine and tube feeding. Within four weeks there was a significant improvement and the patient could be discharged from hospital. The patient is in clinical remission, even after cessation of prednisone.

Case report 2

A second patient report concerns a 17-year-old male who had taken isotretinoin for acne (20 mg three times daily) for a period of six months. He had no medical history of (inflammatory) bowel disease and was in very good health. After discontinuation of isotretinoin he developed an inflammation of the colon and small intestine and abscess. This resulted in hospitalisation six months after isotretinoin cessation. The diagnosis of probable Crohn's disease was made. He was treated with prednisone and mesalazine after which the symptoms improved.

Case report 3

The third case (reported by a general practitioner) concerned a 17-year-old male with no previous medical history, who had taken isotretinoin for a period of six months for the treatment of acne conglobata. Three months after discontinuation of the isotretinoin he developed abdominal pain, bloody diarrhoea and fatigue. After hospitalisation and colonoscopy chronic inflammation of the colon (at the least) was established. In addition he had a cholestatic liver function disorder, most probably primary sclerosing cholangitis (PSC). It should be noted that about 70% of all PSC cases are associated with inflammatory bowel disease, especially ulcerative colitis. The patient was treated with mesalazine and prednisolone. Follow-up on this report, three and a half years later, revealed that the patient was recently found to have inflammatory bowel disease, most likely to be ulcerative colitis.

LITERATURE

Inflammatory bowel disease induced by isotretinoin use has been described in several case reports.[2-4] These case reports relate to teenagers with no previous medical history who developed gastrointestinal symptoms after several weeks to months of isotretinoin treatment, eventually leading to the diagnosis ulcerative colitis[2,3] or proctosigmoiditis.[4]

Over 200 cases of gastrointestinal adverse drug reactions occurring during or after treatment with isotretinoin have been reported to the Federal Drug Administration. These include Crohn's disease and ulcerative colitis. Abnormalities may not appear until months to a year or more after the discontinuation of isotretinoin.[5]

The database of the Uppsala Monitoring Centre of the WHO contains 101 reports on isotretinoin and ulcerative colitis and 35 reports on isotretinoin and Crohn's disease. Both ADRs are statistically significantly more often reported in association with isotretinoin than with other drugs (odds ratio on ulcerative colitis 19.5, 95% CI 15.9 to 24.0; odds ratio on Crohn's disease 18.7, 95% CI 13.1 to 26.5). These findings support the association between isotretinoin and IBD. The views expressed here are purely those of the writer and may not in any circumstances be regarded as a statement on the official position of the WHO.

DISCUSSION

Inflammatory bowel disease (IBD) is defined as an idiopathic and chronic intestinal inflammation. Ulcerative colitis and Crohn's disease are the two major types of IBD. The aetiology and pathogenesis of IBD have not been fully clarified.[6] Both Crohn's disease and ulcerative colitis have a variable course and the peak onset age is between 10 and 30 years. Therefore, it cannot be excluded that the onset of this disease was spontaneous in the adolescents described in this article. On the other hand, all three reporters made the association with the use of isotretinoin, and this association seems to be consolidated by several cases reported worldwide. To our knowledge there is no relationship between acne and IBD.

The mechanism behind isotretinoin-induced inflammatory bowel disease is not fully elucidated. In our view it seems plausible that the inhibition of cell growth, which is effective for the treatment of acne, may be harmful in intestine tissue, where rapid turnover of the intestinal cells is indispensable. Several mechanisms for the effect of synthetic retinoids have been proposed: disturbance of epithelial cell maturation resulting in inflammation, alterations in glycoprotein metabolism compromising the colonic mucosal integrity, and induction of killer T-cell

activity. A fourth hypothesis is that retinoids influence phenotypic expression by colonic epithelial cells, which might serve as a stimulus for an inflammatory response.[4] IBD is considered an immune-modulating disease, with unregulated or excessive T-cell responses to normal stimuli, due to failing counter-regulatory mechanisms.[7,8] In this light, an effect of isotretinoin on IBD could be explained by its proposed effect on T-cell activity in susceptible patients.

With respect to all three patients described in our article, onset of IBD took place after the cessation of isotretinoin use. This finding is in line with the case report described by Reniers and Howard: their patient developed IBD shortly after completion of the treatment with isotretinoin.[3] Also Prokop pointed to the possibility of extended disease latency to diagnosis: he stated that abnormalities may not appear at all until months to a year or more after isotretinoin treatment is terminated.[5] This phenomenon may be due to the fact that the symptoms have their origin in the process of restoration of the original cell growth of the intestinal mucosa. Discontinuation of isotretinoin may induce a disturbed re-growth of the intestinal tissue.

It should be noted that patients with IBD may have a wide range of vague symptoms for several years before the diagnosis is made. Therefore the association with prior isotretinoin use can easily go unnoticed. It may therefore be useful to ask patients who are diagnosed with IBD about possible use of isotretinoin in the past.[5] On the other hand it cannot be excluded that patients diagnosed with IBD during or after use of isotretinoin already had an (unnoticed) pre-existent inflammatory bowel disorder for a longer period of time. In this case, isotretinoin would have been acting merely as the trigger for the eventual manifestation of IBD symptoms.

The reported incidence of this adverse drug reaction is low. With this article we would like to ask for your attention for this alleged association. We would appreciate your reactions, reflecting your personal experience on this subject, either by additional case reports, which strengthen the association between isotretinoin and IBD, or on the other hand by arguments or case reports which speak against this association.

ACKNOWLEDGEMENTS

We would like to thank the reporting physician/patients for their cooperation.

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SPECIAL REPORT

Why the Netherlands Journal of Medicine wants your review article

The Editorial Board

Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

Each issue of the *Netherlands Journal of Medicine* contains a balanced mix of original articles, case reports, reviews and special articles.[1] A well-written review provides the readers with a comprehensive overview on topical issues in the broad field of internal medicine, as well as information of immediate clinical relevance. These articles are highly valued by readers, clinicians and scientists alike.[2] Timely and relevant reviews perhaps organised along medical speciality lines should help to provide a basis for the innovation of medical practice. It is foremost a vehicle for disseminating the latest knowledge in a readily accessible form. This will permit physicians to improve their standard of care for their patients. On the other hand, these articles serve to highlight issues of paradigm and may provide a guide for the caring physician. The Editorial Board of the Journal appreciates good reviews and this appreciation is materialised each year by awarding a prize for the best review article during the *Internistendagen*.[3,4]

The benefits for authors contributing to our Journal are clear. As Editors, we believe that the internet has already induced a paradigm shift in the way in which clinicians and patients access, interpret and utilise medical information. The creation of the open access mode for our Journal last year has greatly broadened our base.[5] Our open access model ensures wide dissemination of important material which becomes freely and universally accessible online. This is why we, as editors of the Journal, invite you to be part of our vision and to submit your review article to the *Netherlands Journal of Medicine*. We will consider articles that span a wide range of scientific interests. In particular, our vision is to include review articles with teaching material, as well as recent developments in pharmacological treatments in order to build a resource for clinicians, whether experienced or otherwise. We look forward to seeing your contributions, which can now be submitted online via our website http://mc.manuscriptcentral.com/nethjmed.[6]

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Netherlands
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ABOUT THE COVER

Untitled

Brigitte Gmachreich-Jünemann

Brigitte Gmachreich-Jünemann, born in Tübingen (1948), now lives and works in Kranenburg, Germany.
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In contrast to all the rush, the bright colours should explore silence. Her work has been appreciated, which has resulted in her receiving several awards such as the Ferdinand Langen-Kulturpreis der Stadt Goch in 1993. In 2001 she won the Arbeitsstipendium der Aldegrever Gesellschaft and in 2004 she was the winner of the 16th 'Sächsisches Druckersymposium' in Leipzig.
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Netherlands
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PHOTO QUIZ

Yellow discolouration

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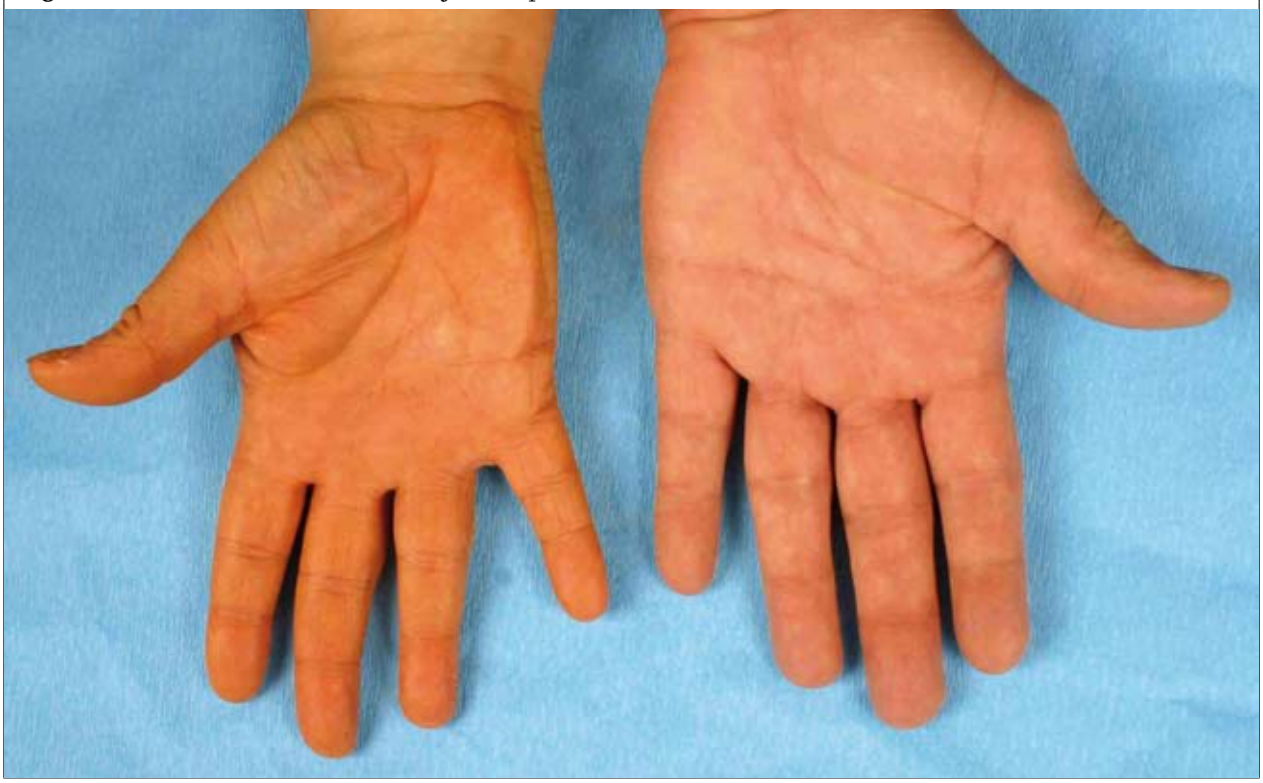
CASE REPORT

A 47-year-old man was hospitalised for erysipelas. Apart from a painful, swollen leg and a fever, he had no other complaints. He had documented diabetes mellitus since 1994. His medication comprised mixtard, rosiglitazone/metformin, atorvastatin and aspirin. On physical examination he was obese with a body weight of 146 kg. His right leg showed signs of erysipelas and he had a striking yellow discolouration of his skin. The discolouration was most prominent on the palms of his hands (*figure 1*) and the plantar sides of his feet. His sclerae were not discoloured and the serum bilirubin level was normal.

WHAT IS YOUR DIAGNOSIS?

See page 57 for the answer to this photo quiz.

Figure 1. *Yellow discolouration on the left hand palm*



ANSWER TO PHOTO QUIZ (ON PAGE 56)

YELLOW DISCOLOURATION

DIAGNOSIS

The localisation of the yellow discolouration without involvement of the sclerae suggested the diagnosis of hypercarotenaemia. The dietary intake of this obese man consisted of two large cans of vegetables at breakfast, one small tin of vegetables with two peanut butter sandwiches at lunch and between meals six tomatoes, two oranges and three apples. At dinner he ate two eggs, 500 g of green beans and one large can of vegetables. High-performance liquid chromatography revealed an increased serum β-carotene at 1.16 μmol/l (0.07 to 0.88), with a normal vitamin A of 1.64 μmol/l (0.69 to 2.79) levels. Porphyria and hypothyreoidism, which increases the susceptibility for hypercarotenaemia, were excluded. His medical history of diabetes mellitus type 2 may add to the carotenaemia. However, in this case, the high intake of vegetables is the primary cause. Toxicity of β-carotene is considered low, but there are insufficient safety data on β-carotene suppletion. The suggestion that β-carotene may reduce the risk of cancer is derived from epidemiological studies, but could not be confirmed by clinical trials, which even showed harmful effects in smokers.[1,2] When the intake of vegetables is normalised, serum carotene levels return to normal.

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Aims and scope

The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the editor are welcomed.

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Manuscripts submitted to the Journal should report original research not previously published or being considered for publication elsewhere. Submission of a manuscript to this Journal gives the publisher the right to publish the paper if it is accepted. Manuscripts may be edited to improve clarity and expression.

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The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

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Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process, number the lines in the margin and the pages.

Subheadings should not exceed 55 characters, including spaces.

Abbreviations: Measurements should be abbreviated according to SI units. All other abbreviations or acronyms should be defined on the first appearance in the text. Use a capital letter for generic names of substances and materials.

A *Covering letter* should accompany the manuscript, identifying the person (with the address, telephone number, fax number and e-mail address) responsible for negotiations concerning the manuscript. The letter should make it clear that the final manuscript has been seen and approved by all authors. Conflicts of interest, commercial affiliations, consultations, stock or equity interests should be specified. In the letter one to three sentences should be dedicated to what this study adds. All authors should sign the letter.

Divide the manuscript into the following sections: Title page, Abstract, Keywords, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

The *Title page* should include authors' names, degrees, academic addresses, correspondence address, including telephone number, fax number, e-mail address and grant support. Also the contribution of each author should be specified.

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The *Abstract*, not exceeding 250 words, should be written in a structured manner and with particular care. In original articles, the Abstract should consist of the following paragraphs: Background, Methods, Results and Conclusion. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

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2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
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