

Reply

EDITOR—We thank Drs Heaton and Emmett for their interest in our paper (*Gut* 2000;47:144–7) and the insightful comments. We regret not having cited their previous research findings on the relationship between plasma insulin and prevalent gall stones.1 We agree that waist to hip ratio may be an important variable to consider. However, waist to hip ratio and insulin are intimately related in the pathophysiological pathways linking insulin resistance to gall stone formation, therefore the interpretation of results from analytical models, including both of these variables, may be problematic. In addition, we concur with the potential importance of physical fitness, and would like to add that physical activity may also play a role in the aetiology of gall stones. Our conclusion is based on the findings from a previous paper by our group showing a strong association between physical activity and incident gall stones in a population based case control study.2

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Heparin as an anti-inflammatory agent: it’s no GAG to forget about chemokines

EDITOR—We approached with enthusiasm the report by Salas and colleagues (*Hepatol* 2000;31:745–51) that heparin is an anti-inflammatory agent: “It’s no GAG to forget about chemokines”.3 However, the authors’ selective invocation of potential explanations for heparin as an anti-inflammatory agent, while an effect of heparin on the neutrophil integrin adhesion molecule CD11b was described in elegant studies, heparin almost certainly exerts its anti-inflammatory effects through a range of activities beyond an adhesion molecule target. One of these targets is the superfAMILY of cytokines known as chemokines, metabolism of which is crucial to the recruitment and homeostasis of leucocytes. They have a capacity to bind selectively to a range of glycosaminoglycans, or GAGs, including heparin, in tissues and on the surface of both endothelial cells and leucocytes. This interaction heightens migration along a fixed gradient, or so-called haptotaxis,4 and favours receptor binding.5 There is strong evidence that soluble GAGs, including heparin, prevent chemokines binding to their receptors, thus abating their chemotactic potential.6 Neither Salas and colleagues nor Perretti and Page chose to mention an anti-chemokine mechanism for the anti-leucocyte migration activity of heparin. We ignore chemokines at our peril though, as their sheer number and abundance, and the intensity of the effort being directed at discovering pharmacological inhibitors of their function, highlight their critical role in inflammation.

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Management of varical haemorrhage in cirrhotic patients

EDITOR—We have serious concerns about several of the recent UK guidelines for the management of varical haemorrhage in cirrhotic patients (*Gut* 2000;46(suppl 3 and 4))iiili–iii115), particularly those that contradict current published evidence. We highlight below the ones we feel are the most important.

In the management of acute varical bleeding, vascular occlusion remains the method of first choice which was given an AI recommendation. Meta-analysis of all trials of acute bleeding of banding versus injection sclerotherapy have shown no statistically significant difference between the two treatments for either control of bleeding or survival (data derived from 12 studies with 419 patients), with no statistical heterogeneity. The implication of recommending ligation for acute bleeding is that double intubation would be necessary in a patient who is actively bleeding so as to attach the ligation device after the initial diagnostic endoscopy. Although we have no evidence, this would create more risk to the patient; it is common sense that a single intubation would be preferable and would take less time. At best the recommendation should be that either endoscopic technique could be used as first choice, dependent on operator expertise and facilities.

Secondly, there is evidence from randomised studies of vasoactive drug therapy combined with endoscopic techniques that combination therapy is superior in terms of control of bleeding. This is based on five randomised studies with 610 patients (pooled odds ratio 0.42, 95% confidence interval 0.29–0.6).7 Publication bias assessment has shown that 29 null or negative studies would be needed to render the results non-significant, and thus this efficacy is fairly robust. Moreover, in several of these studies vasoactive drugs were given before diagnostic endoscopy, demonstrating their utility during the period of resuscitation before endoscopy could be safely performed, which in practice may be several hours after admission. This goes against the recommendation that drugs can be used if endoscopy is not available. Drugs should be used first followed by therapeutic endoscopy.

As regards the prevention of rebleeding from sources due to portal hypertension, the treatment of first choice, unless there are contraindications, is either non-selective β blockers as they are equipotent therapy,8 or band ligation. No fully published randomised studies are available with regard to β blockers versus banding. If banding is not available, β blockers should be used, not sclerotherapy, as recommended by the guidelines as contraindications or intolerance to β blockers, banding should be used. One can argue cogently that as non-selective β blockers are cheap and do not involve repeated endoscopy sessions, they always should be considered the treatment of first choice.

The recommendation of measuring hepatic venous pressure gradient (HVPG) in patients given β blockers cannot be one for current practice. Only two Spanish groups have suggested this, and it is unclear when a repeat measurement should be performed. Moreover, both a 20% reduction from baseline HVPG or an absolute HVPG of less than 12 mm Hg are “protective” from rebleeding, so both end points, and not just the absolute reduction, need to be mentioned if this management strategy is used. In any case the randomised study of vasoactive drug therapy used non-selective β blockers empirically to the maximum tolerated by patients so that drugs of without pressure measurement was effective. Lastly, if the recommendation of using drugs with re-measurement of pressure is taken to its logical conclusion, all patients should be tried on drugs first, as those who respond have far less rebleeding (10% or less) than patients who receive banding, and secondly, a recommendation of what to do next would need to be made for those who do not reduce their portal pressure (for which as yet there is no evidence). Lastly, two meta-analyses comparing TIPS with endoscopic techniques demonstrated that TIPS did not improve survival.9,10 The increased encephalopathy, greatly increased cost, as well as poor availability of TIPS treatment does not make it a first choice treatment for rebleeding, even in centres with expertise such as the authors’ own, as stated in the guidelines. Thus the AI recommendation grading is particularly inappropriate.

With respect to primary prevention of portal hypertensive bleeding in cirrhosis, we