Influence of IL-6, COL1A1, and VDR gene polymorphisms on bone mineral density in Crohn’s disease

C E Todhunter, A Sutherland-Craggs, S A Bartram, P T Donaldson, A K Daly, R M Francis, J C Mansfield, N P Thompson

Background: Osteoporosis is an important cause of morbidity in patients with Crohn’s disease. The pathogenesis of reduced bone mineral density (BMD) is multifactorial. A range of genetic factors have been implicated in other populations of patients with osteoporosis.

Aim: To investigate the influence of interleukin 6 (IL-6), collagen type 1α1 (COL1A1), and vitamin D receptor gene (VDR) single nucleotide polymorphisms (SNP) on BMD in patients with Crohn’s disease.

Patients: A cohort of 245 well characterised patients with Crohn’s disease were recruited from the inflammatory bowel disease register at the Freeman Hospital and Royal Victoria Infirmary, Newcastle upon Tyne, and the Queen Elizabeth Hospital, Gateshead, UK.

Methods: Patients were genotyped for IL-6 C-174G SNP, COL1A1 Sp1 binding site G T SNP, VDR Taq1, and Fok1 SNPs, and CARD15 R702W, G908R, and L1007fs SNPs. BMD was measured at the lumbar spine (LSP) and hip using dual energy x-ray absorptiometry.

Results: A total of 158 female and 87 male patients, aged 24–70 years (mean 44), were recruited. There were no significant differences in the distribution of the tested SNPs when analysed for age, body mass index, pre/post-menopausal status, smoking, or steroid use. Two hundred and thirteen patients were genotyped for the IL-6 SNP. LSP and total hip BMD was significantly lower in patients with the GG genotype (48%) than the CC genotype (15%) (p = 0.041, p = 0.014). One hundred and eighty patients were genotyped for the COL1A1 SNP. There was no significant difference in BMD at LSP. Hip BMD was significantly lower in heterozygous patients compared with homozygous wild-types (p = 0.034). There were no significant differences in BMD between genotypes for the two VDR SNPs or the CARD15 genotypes examined.

Conclusion: IL-6 and COL1A1 gene polymorphisms influence BMD in patients with Crohn’s disease but the particular VDR gene polymorphisms studied do not have a major effect.
The SNPs investigated were: the FokI and TaqI polymorphisms of VDR, the G to C SNP at position −174 of IL-6, and a polymorphism at the Sp1 transcription factor binding site of COL1A1.

Polymorphisms in the CARD15 gene on chromosome 16 have been identified as susceptibility markers for Crohn’s disease and are known to be associated with ileal disease rather than purely colonic disease. Osteoporosis is a complication of severe Crohn’s disease; we investigated whether CARD15 mutations are associated with BMD.

PATIENTS AND METHODS

Patients were recruited from the inflammatory bowel disease register at the Freeman Hospital and the Royal Victoria Infirmary, Newcastle upon Tyne, and the Queen Elizabeth Hospital, Gateshead, UK. All patients had a diagnosis of Crohn’s disease and were under the care of either surgical or medical gastroenterologists and were diagnosed by a combination of radiology, endoscopy, and biopsy. Only patients aged 24–70 years were included, and women who were pregnant or planning a pregnancy were excluded because of the potential risk from exposure to ionising radiation during bone densitometry. Initial demographic data were collected by questionnaire, including age, smoking history, and reproductive and menstrual history in women. Details regarding the use of disease, corticosteroid use in months, and surgical and drug history were obtained through direct interview and from the medical notes. Prior to bone densitometry, height and weight were measured and BMI calculated. All patients gave informed consent to participate. The Newcastle upon Tyne joint ethics committee granted ethics approval.

For comparison, when testing the hypothesis that the VDR genotype is associated with Crohn’s disease, a geographically and racially matched cohort of healthy controls was recruited from in vitro fertilisation donors and healthcare workers.

BMD measurement

BMD was measured at the lumbar spine (LSP) and total left hip using dual energy x-ray absorptiometry (QAR 2000; Hologic Inc., Waltham, Massachusetts, USA), as previously described. Osteoporosis is defined by the WHO as a bone density of 2.5 or more standard deviations below the mean value for young adults, and osteopenia as a T score of −1 to −2.5 at any site. Classification as normal BMD, osteopenic, or osteoporotic is dependent on the site with the lowest BMD T score.

Genotyping

Determination of VDR TaqI genotype

A 340 bp fragment, which included the site of the T to C polymorphism at codon 352 in exon 9 of the VDR gene on chromosome 12, was amplified in a 25 μl reaction mixture containing 200 μM each of dATP, dCTP, dGTP, and dTTP (ABGene, Surrey, UK), 10 mM Tris-HCl, pH 8.3, 50 mM KCl, 0.01% gelatin, 1 U Taq Polymerase (ABGene), 0.5 μM of each primer, and 1 μl (approximately 0.2–0.5 μg) of template DNA on a Perkin-Elmer GeneAmp 9700. The alleles relating to this polymorphism are designated “t” (TaqI site present) or T (TaqI site absent).

The primers used were: 5’ CAG AAG ATg gAC Agg gAC CAA g’-3’ forward and 5’ ggg TgT gAC gCA TCT gCA gTg Tg-3’ reverse (Oswel, Southampt, UK).

Following amplification, 15 μl of the product were digested with 2.5 units of TaqI (ABgene) at 65°C. Digested restriction fragments were separated on 2.5% (w/v) agarose (Sigma, Poole, Dorset, UK) gels, with 1×Tris-Borate-EDTA (TBE) running buffer (Sigma) Samples of known genotype were run as controls and a water negative (DNA free) control in each batch.

Bands were visualised on an Alpha Innotech Imager system and assigned as follows: T/T 340 bp only; T/t 340 bp, 293 bp, and 47 bp; t/t 293 bp and 47 bp.

Determination of VDR FokI genotype

A 265 bp fragment, which includes the site of a C to T polymorphism at the start codon, was amplified as above. The alleles which result from this change are designated “f” (FokI site present) or “F” (FokI site absent).

The primers used were: 5’ ACA Tgg CCC Ttg CAC TgA TCT TgC TCT-3’ forward and 5’ ATg gAA ACA CCT TgC TTC TTC TgC TCC TCT-3’ reverse (Oswel).

The PCR amplification conditions were as follows: initial denaturation at 94°C for five minutes followed by 32 cycles of 94°C for 45 seconds, 58°C for 45 seconds, followed by 72°C for 45 seconds, and a final extension at 72°C for seven minutes.

Following amplification, 15 μl of the product were digested with 4 units of FokI restriction endonuclease (ABgene) at 37°C. Digested restriction fragments were separated on 2% (w/v) agarose (Sigma) gels as described above. Genotypes were assigned as follows: F/F 265 bp only; F/f 265 bp, 169 bp, and 96 bp; f/f 169 bp and 96 bp.

Determination of IL-6 – 174 genotype

A 431 bp fragment, which includes the site of a G to C polymorphism at position −174 in the promoter region of the IL-6 gene, was amplified as above. On digestion with NlaIII, the wild-type sequence with G at position −174 is not digested whereas a C at −174 creates a restriction site for NlaIII and is digested. The primers used were: 5’ CAg AAg AAC TCA gAT gAC Tgg-3’ forward and 5’ gTg ggg Ctg ATT ggg AAC C-3’ reverse (Oswel).

The PCR reaction conditions for amplification were as follows: initial denaturation at 95°C for five minutes followed by five cycles of 95°C for 30 seconds, 58°C for 60 seconds, followed by 72°C for 60 seconds, followed by 25 cycles of 95°C for 30 seconds, 56°C for 60 seconds, followed by 72°C for 60 seconds, followed by five cycles of 95°C for 30 seconds, 54°C for 60 seconds, followed by 72°C for 60 seconds and a final extension at 72°C for seven minutes.

Following amplification, 15 μl of the product were digested with 2.5 units of NlaIII restriction endonuclease (ABgene) at 37°C. Digested restriction fragments were separated on 2% (w/v) agarose gels, as described above. For the various genotypes, the following band patterns were obtained: G/G 229 bp, 173 bp, and 29 bp; G/C 229 bp, 173 bp, and 122 bp; C/C 229 bp, 122 bp, 51 bp, and 29 bp.

Determination of COL1A1 genotype

A 280 bp fragment, which included the site of the G T polymorphism at the Sp1 binding site in the first intron of COL1A1 gene, was amplified as above. The primers used were: 5’ CTG GAC TAT TTG CGG ACT TTT TGG-3’ forward and 5’ CTg gAC TCT gCA gTg Tg-3’ reverse (Oswel).

The PCR amplification conditions were as follows: initial denaturation at 94°C for six minutes followed by 30 cycles of 94°C for one minute, 64°C for one minute, and 72°C for one minute.

Following amplification, 10 μl of the product were digested with 1 unit of MseI restriction endonuclease (New England Biolabs) at 37°C. Digested restriction fragments were separated by polyacrylamide gel electrophoresis on 10%
Table 1  Patient demographics

<table>
<thead>
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<tbody>
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<tr>
<td>Age (y)</td>
<td>44.4 (11.4) (24-70)*</td>
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<tr>
<td>Post menopausal</td>
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</tr>
<tr>
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<td>28</td>
</tr>
<tr>
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</tr>
<tr>
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<td>Never</td>
<td>28</td>
</tr>
<tr>
<td>Previous use</td>
<td>144</td>
</tr>
<tr>
<td>Current steroids</td>
<td>73</td>
</tr>
<tr>
<td>Duration of steroids (months)</td>
<td>45 (66.4) (0-372)*</td>
</tr>
<tr>
<td>Duration of disease (y)</td>
<td>14.3 (9.5) (0.5-50)*</td>
</tr>
</tbody>
</table>

*Values are mean (SD) (range).

polyacrylamide gels, with 1×TBE running buffer (Sigma). Samples of known genotype were run as controls, and water as a negative (DNA free) control in each batch.

Following electrophoresis for four hours at 160 mV, bands were visualised on an Alpha Innotech Imager system. The patterns corresponding to the various genotypes were as follows: homozygous wild-type (GG) 280 bp only; heterozygous (GT) 280 and 260 bp; and homozygous mutant (TT) 260 bp only.

CARD15 genotyping

This was performed as previously reported in Cuthbert and colleagues27 in Professor C Mathew’s laboratory, Department of Medical and Molecular Genetics, Guy’s, Kings and St Thomas’ School of Medicine, London, UK. In brief, genotypes of the polymorphisms R702W, G908R, and 3020insC were determined using the TaqMan biallelic discrimination system. This was performed as previously reported in Cuthbert and colleagues27 in Professor C Mathew’s laboratory, Department of Medical and Molecular Genetics, Guy’s, Kings and St Thomas’ School of Medicine, London, UK. Primers for exon amplification were designed on the basis of the Genbank sequence NT_019610.

Statistical analysis

To look for differences in BMD at the hip and LSP between genotypes, ANOVA was employed. Where this was significant, Tukey’s test for multiple comparisons was used to compare differences between groups. Multiple regression analysis was used to determine additional risk of steroid use and genotype.

RESULTS

Baseline characteristics

A total of 245 patients with Crohn’s disease were studied (table 1): 54 (22%) were osteoporotic at any site, 106 (43%) were osteopenic at any site, and 160 (65%) had normal bone density. There were no significant differences between any genotypes and age, BMI, pre/post menopausal, smoking, or steroid use (data not shown). All controls were residents of the North Tyneside-Newcastle region of North East England and all were of Northern European Caucasian ancestry. None had a history of autoimmune disease or inflammatory bowel disease.

Genotype

All genotypes were in Hardy-Weinberg equilibrium. Genotype distributions are shown in table 2. Comparing genotype distribution of COL1A1, IL-6, and VDR Fok1 with those of 257 healthy controls, there were no statistically significant differences. There was no difference in VDR Taq1 genotype frequency between patients with Crohn’s disease and controls (p = 0.10). Control genotype frequency was CC 40 (15%), TC 115 (45%), and TT 102 (40%).

Genotype and bone mineral density

VDR Taq1

There was no significant difference in BMD at the LSP or hip between VDR Taq1 genotypes. There was also no difference in T score at the LSP and hip and VDR Taq1 genotype (table 3).

VDR Fok1

There was no significant difference in BMD at the LSP or hip between VDR Fok1 genotypes. There was also no difference in T score at the LSP and hip and VDR Fok1 genotype (table 3).

IL-6

At the LSP there was a significant difference in BMD between IL-6 genotypes (p = 0.041). This difference was between the GG and CC genotypes by pairwise comparison allowing for multiple testing. The CC genotype had a higher mean BMD (1.03 g/cm²) than the GG genotype (0.95 g/cm²) (95% confidence interval for the difference (CI) 0.0032–0.1524). There was only a trend towards significance between T score and genotype (p = 0.065) (table 3). At the hip there was a significant difference in BMD between IL-6 genotypes (p = 0.014) (table 3, fig 1). The CC genotype had a higher mean BMD of 0.93 g/cm² compared with the GG genotype (mean BMD 0.48 g/cm²; 95% CI 0.0186–0.159). The difference between genotype groups when BMD was expressed as T score was statistically significant (p = 0.013). Mean T score was −0.709 for CC genotype and −1.37 for GG genotype (95% CI 0.119–1.208).

COL1A1

There was no significant difference in LSP BMD between COL1A1 genotypes (p = 0.144). There was also no significant difference in T score at the LSP between genotypes (p = 0.24) (table 3). At the hip there was a significant difference in BMD between COL1A1 genotypes (p = 0.034) (table 3, fig 2). This was between the homozygous wild-type (GG) and heterozygous (GT) genotypes. Mean BMD for the GG genotype was 0.88 g/cm² and for GT 0.81 g/cm² (95% CI 0.0051–0.1307). There was also a significant difference in T scores between genotypes (p = 0.025). Again, the GG genotype had a higher T score (−1.03) than the GT genotype (−1.59; 95% CI 0.066–1.063).

Genotype steroid interaction

Using adjusted r², the variation in BMD at the hip due to duration of steroid use was 5.1%. An additional non-significant variation due to genotype was 1.2% (p = 0.09). However, there was a significant additional reduction in BMD at the hip with IL-6 GG genotype compared with CC of 5.3% (95% CI 10.4–0.2%; p = 0.04). There was no significant effect of GC genotype compared with CC genotype.

There was also a significant reduction in BMD at the hip with COL1A1 GT genotype compared with GG of 5.8% (95%
CI 11.2–0.4%; p = 0.035) There was no significant effect of TT genotype compared with GG genotype.

There was no significant additional change in LSP BMD with IL-6 of COL1A1 genotypes.

CARD15
There was no significance in BMD or T score between CARD15 genotypes (table 2). The frequencies of CARD15 genotypes are shown in table 2. As expected, there was a higher frequency of CARD15 mutations in the Crohn’s disease population than the control group (n = 104): wild-type 77 (91%), heterozygote 7 (7%), and homozygote 0.

DISCUSSION
This was a large study of the relationship between genes and BMD in a well characterised population of patients with Crohn’s disease. When analysed by genotype there was no difference in duration of disease, steroid use, age, BMI, or smoking status, allowing valid comparisons between genotypes to be made.

A significant association was found between IL-6 polymorphisms and lower BMD at the LSP and hip in patients with Crohn’s disease. The largest difference was seen at the hip where the GG (49%) genotype had a 9.6% lower mean BMD than the CC (15%) genotype; at the LSP there was a 7.5% difference. From the analysis, the C allele appears to produce a protective effect as the GC heterozygote had a significantly higher BMD than the GG homozygote.

The finding of an association between IL-6 polymorphisms and BMD in Crohn’s is consistent with previous work. Schulte and colleagues studied 83 patients with a mixture of Crohn’s disease and ulcerative colitis. IL-6 polymorphisms have also been associated with lower BMD in post-menopausal

![Figure 1](image1.jpg)  Mean bone mineral density (BMD) in the different interleukin 6 (IL-6) genotype groups. 95% CI, 95% confidence interval.

![Figure 2](image2.jpg)  Mean total hip bone mineral density (BMD) in the different collagen type 1α1 (COL1A1) genotype groups. 95% CI, 95% confidence interval.

| Table 3 Bone mineral density (BMD) for each genotype |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Genotype          | LSP BMD (g/cm²) | LSP T score     | Total hip BMD (g/cm²) | Hip T score     |
| VDR Taq1          |                 |                 |                 |                 |
| CC                | 0.98 (0.13)     | -0.73 (1.19)    | 0.86 (0.15)     | -1.15 (1.20)    |
| TC                | 0.98 (0.16)     | -0.70 (1.47)    | 0.87 (0.15)     | -1.12 (1.25)    |
| TT                | 0.96 (0.15)     | -0.95 (1.44)    | 0.84 (0.15)     | -1.29 (1.17)    |
| VDR Fok1          |                 |                 |                 |                 |
| ff                | 0.95 (0.18)     | -1.04 (1.67)    | 0.85 (0.19)     | -1.30 (1.54)    |
| FF                | 0.97 (0.15)     | -0.80 (1.41)    | 0.85 (0.14)     | -1.21 (1.15)    |
| FF                | 0.95 (0.15)     | -0.65 (1.35)    | 0.89 (0.15)     | -1.05 (1.16)    |
| IL-6              |                 |                 |                 |                 |
| CC                | 1.03 (0.15)*    | -0.33 (1.41)    | 0.93 (0.14)*    | -0.71 (1.03)*   |
| GC                | 0.99 (0.17)     | -0.69 (1.50)    | 0.87 (0.14)     | -1.06 (1.09)    |
| GG                | 0.95 (0.15)     | -0.98 (1.37)    | 0.86 (0.15)     | -1.37 (1.25)    |
| COL1A1            |                 |                 |                 |                 |
| GG                | 0.98 (0.14)     | -0.75 (1.33)    | 0.88 (0.15)     | -1.03 (1.19)    |
| GT                | 0.94 (0.15)     | -1.15 (1.39)    | 0.81 (0.14)*    | -1.59 (1.18)*   |
| TT                | 0.99 (0.16)     | -0.59 (1.51)    | 0.87 (0.15)     | -1.08 (1.27)    |
| CARD15            |                 |                 |                 |                 |
| Wild-type         | 0.98 (0.15)     | -0.77 (1.05)    | 0.87 (0.15)     | -1.14 (1.22)    |
| Heterozygote      | 0.96 (0.17)     | -0.89 (1.50)    | 0.85 (0.15)     | -1.26 (1.14)    |
| Homozygote        | 0.97 (0.16)     | -0.95 (1.44)    | 0.88 (0.17)     | -1.27 (1.23)    |

Values are mean (SD). IL-6, interleukin 6; COL1A1, collagen type 1α1; VDR, vitamin D receptor; LSP, lumbar spine. *p < 0.05.
women\(^{26}\) and with lower peak bone mass in healthy males.\(^{27}\) However, in another study of 75 patients with Crohn’s disease from a cohort of 105 patients with inflammatory bowel disease, no association was found between IL-6 polymorphism and BMD.\(^{33}\) This last study however was smaller than the present investigation and BMD was expressed as Z score only, rather than as absolute BMD. In addition, the effect of IL-6 seen in the present investigation was relatively small and the earlier study was significantly underpowered by comparison.

IL-6 is thought to be involved in bone remodelling and hence development of osteoporosis through stimulation of osteoclast development and regulation of bone resorption.\(^{10,23,34}\) Higher levels of IL-6 have been found in patients with Crohn’s disease\(^{10}\) and serum levels of IL-6 have been found to predict bone loss in post-menopausal women.\(^{31}\) Studies in vitro have shown that the CC IL-6 genotype results in lower stimulated IL-6 promoter activity and in vivo with lower levels of plasma IL-6.\(^{32}\) In post-menopausal women, the CC IL-6 polymorphism was found to be associated with lower bone resorption and less of a loss in BMD compared with the GG genotype.\(^{36}\) It is possible that in Crohn’s disease, a chronic inflammatory condition that results in higher serum levels of IL-6, the CC genotype is protective against IL-6 mediated bone resorption.

This study found a significantly lower BMD at the hip in Crohn’s disease patients with the heterozygous COL1A1 (27%) genotype compared with the homozygous wild-type (53%).\(^{15}\) The TT homozygous genotype resulted in a 6% reduction in BMD. At the hip there was also a significant reduction in T score to a level below that where therapy is recommended in glucocorticoid induced osteoporosis.\(^{37}\)

This study is in agreement with other published work on COL1A1 gene polymorphisms. COL1A1 gene polymorphisms have been associated with low BMD and fractures in other populations.\(^{22,24}\) A recent meta-analysis involving 6800 subjects also found a significantly lower BMD at the lumbar spine in the heterozygous group compared with the homozygous wild-type but no significant difference in the homozygous TT group.\(^{21}\)

COL1A1 gene polymorphisms at the Sp1 binding site are thought to be functional, altering the level of transcription and production of collagen and therefore the physical properties of bone.\(^{25}\) Osteoblasts derived from heterozygote subjects were found to have altered production of the collagen 2(1) chain relative to the 2(2)(1) compared with wild-type individuals. The same study found that bone strength was reduced in heterozygotes compared with wild-type subjects.

In this analysis there was no association between BMD and either two of the VDR SNPs studied. A meta-analysis of 16 studies in 1996 found a small effect for VDR polymorphisms,\(^{38}\) with a 2.4% difference in BMD between genotypes. Such a small effect has limited clinical significance. The numbers in this study were adequate to detect a difference of 4–5% between genotypes.

A significant additional effect was found between duration of steroid use and IL-6 GG genotype as well as COL1A1 heterozygotes. This effect however was small. It would be useful to be able to comment on the interaction of the different genotypes but this study did not have sufficient numbers to allow that comparison to be made. Further research is needed to investigate whether there is a different response to the treatment of osteoporosis between genotypes.

No association was found in this study between VDR Taq1 polymorphism and susceptibility to Crohn’s disease. This is in contrast with previous published data of 245 patients with Crohn’s who were found to have an increased frequency of the Tt genotype (synonymous with CC in this study).\(^{13}\) The results here are in agreement with a small study of 95 patients with Crohn’s disease in which no association was found.\(^{39}\)

Multiple risk factors for development of osteoporosis have been identified, including BMI and steroid use.\(^{2}\) Many studies have found an increased risk of fracture in patients with Crohn’s disease\(^{1,10,40,41}\) although this is not consistent.\(^{42,43}\) Development of risk stratification by genotype as well as clinical risk may enable targeted treatment with agents such as pamidronate\(^{44}\) or other bisphosphonates\(^{45}\) or calcium supplements,\(^{46}\) dependent on risk. Patients could be tested prior to corticosteroids for example and those at greater risk of developing osteoporosis be targeted with more aggressive screening and treatment. Crohn’s disease patients are younger than other disease groups previously studied and therefore earlier identification of those at risk has potential to be therapeutically important.

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Conflict of interest: None declared.

REFERENCES


EDITOR’S QUIZ: GI SNAPSHOT

Answer

From question on page 1535

Abdominal x ray showed dilated loops of the small bowel with a metal oesophageal stent in the left iliac fossa. The suspicion of stent ileus was confirmed by computed tomography (fig 2) which showed dilated loops of small bowel proximal to the stent. A minilaparotomy was performed which found the small bowel to be dilated down to the site of impaction of the oesophageal stent in the terminal ileum. Unfortunately, the patient developed pneumonia after operation and died three days later.

Stent migration is a recognised complication of oesophageal stenting, occurring in up to 35% of treated patients. It occurs more frequently if the stent is placed across the gastro-oesophageal junction. Provided the patient is asymptomatic, a “wait and see” approach is often reasonable for those with a migrated stent. Indeed, it is unusual for the migrated stent to be passed spontaneously in stool. Endoscopic retrieval of the stent may be possible if it lies within the stomach. Open surgical removal of the migrated stent is reserved for cases of bowel obstruction or perforation.

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Figure 2  Computed tomography scan of the patient. The small bowel is dilated down to the level of the impacted stent. The large bowel is normal.

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