C-reactive protein and migraine. Facts or speculations?

Abstract: Migraine is a highly prevalent and frequently disabling disorder. Since the pathogenesis of this condition has a strong inflammatory component and migraine is significantly associated with cardiovascular disease, we assess whether C-reactive protein (CRP) may be epidemiologically or casually linked with migraine. An electronic search on Medline, Scopus and Web of Science produced 17 studies reporting original data about the epidemiological association between CRP and migraine (1 retrospective, 1 interventional, 14 cross-sectional and 1 both interventional and cross-sectional). When all studies reporting sufficient data about CRP values were pooled (n=12; 6980 cases and 38,975 controls), the concentration of CRP was found to be significantly higher in patients with migraine than in controls (weighted mean difference 1.12 mg/L; 95% CI 1.01–1.25 mg/L; p<0.001). In further analysis of studies containing separate data for migraine with and without aura (n=7), CRP values remained significantly higher in both migraineur patients with aura (n=1939; weighted mean difference 0.88 mg/L; 95% CI 0.63–1.14 mg/L; p<0.001) or without aura (n=2483; weighted mean difference 1.04 mg/L; 95% CI 0.78–1.30 mg/L; p<0.001) when compared with controls (n=29,354). Despite a large inter-study heterogeneity (99.3%), our analysis provides evidence of a potential epidemiological association between increased concentration of CRP and migraine, thus paving the way for further clinical investigations about therapeutic agents that may contextually decrease the risk of cardiovascular disease and reduce the burden of migraine.

Keywords: C-reactive protein (CRP); headache; inflammation; migraine.

Introduction

Migraine is a global disabling condition, which generates remarkable individual frustration and sufferance, thus affecting the quality of life of adults, as well as that of children and adolescents. It has been estimated that 12%–15% of adults suffer from this disease in occidental countries, with a prevalence that is nearly three times higher in the female gender [1]. In a recent meta-analysis of 64 cross-sectional studies including 227,249 children or adolescents, the mean estimated prevalence of migraine in this patient population was 9.1% (95% CI 7.1%–11.1%) [2]. Taken together, these figures make migraine one among the most prevalent human disorders.

According to the 3rd edition (β version) of the International Classification of Headache Disorders recently released by the Headache Classification Committee of the International Headache Society (IHS), migraine is considered a primary form of headache that manifests as pain typically located above the orbitomeatal line [3]. This disorder is typically classified in two leading forms, i.e., migraine with or without aura, with the former condition affecting nearly one third of all migraineur patients. The aura is conventionally defined as manifestations of focal cerebral dysfunction accompanied by early symptoms that precede an attack of migraine and last approximately 20–30 min [3]. Recent insights into the pathogenesis suggest that migraine should be considered a primary neurovascular disorder, where reduced cerebral blood flow (hypoxia), reactive arterial vasodilation (hyperemia), neurogenic inflammation and decreased inhibition of central pain transmission coexist [4]. The development of cortical spreading depression (CSD), which is conventionally defined as a depression of electroencephalographic (EEG) activity moving across the cortex at a rate of 3–6 mm/min, is the biological hallmark that differentiates migraine with aura from that without [5].
Several lines of evidence now attest that inflammation plays a crucial role in the pathogenesis of migraine, wherein a number of proinflammatory cytokines are actively released during migraine and are then involved in a complex process of sensitization of nerve endings in meninges, thus promoting or amplifying the feeling of pain [6]. It has also been recently shown that the risk of cardiovascular disease is substantially increased in patients with migraine. In a recent systematic review and meta-analysis of the current scientific literature including 25 studies, Schürks estimated that migraine confers relative risks of 1.73 (95% CI 1.31–2.29) for ischemic stroke and 1.12 (95% CI 0.95–1.32) for myocardial infarction, respectively [7]. In another, more recent meta-analysis, Rist et al. reported that patients with migraine have a nearly doubled risk of cervical artery dissection, with a pooled odds ratio (OR) of 2.06 (95% CI 1.33–3.19) [8]. As such, the fact that the pathogenesis of migraine has a strong inflammatory component combined with evidence that migraine is significantly associated with cardiovascular disorders, disclose a novel and intriguing scenario. Among the various inflammatory biomarkers, C-reactive protein (CRP) has been strongly associated with a variety of ischemic and thrombotic disorders, including coronary heart disease (CHD) [9], stroke [9], and venous thromboembolism (VTE) [10]. It is hence reasonable to investigate whether this important biomarker may be also epidemiologically or casually linked to migraine.

Search criteria

With the aim to review clinical and epidemiological evidence about the association between migraine and CRP, we searched Medline, Scopus and Web of Science using the keywords “migraine” and “C Reactive Protein” or “CRP”, with no language or date restriction. The references of retrieved items were also searched for identifying additional articles about this topic. Only those articles using standardized criteria for diagnosing migraine (e.g., those of the IHS) and reporting original data about the epidemiological association between CRP and migraine were finally included.

Overview on epidemiological data

The electronic search performed according to the previously defined criteria produced 135 items after elimination of duplicates. Careful reading of title, abstract and full text (when available), allowed to exclude 118 articles, which did not report original data about the epidemiological association between CRP and migraine, or did not use standardized criteria for diagnosis of migraine. Therefore, 17 clinical studies were finally included in this review, i.e., one retrospective, one interventional, 14 cross-sectional and one both interventional and cross-sectional (Table 1) [11–27]. Demographical information, along with the techniques used for measuring CRP [i.e., conventional or high-sensitivity (HS)], were reported, whenever available.

The very first study exploring the association between CRP values and migraine was published by Welch et al. in 2006 [11]. The authors performed a retrospective study based on a review of 60 randomly sampled charts of migraineur patients with (n = 31; 2 males and 29 females; mean age 49 ± 13 years) or without aura (n = 29; 4 males and 25 females; mean age 49 ± 11 years), and for whom measurement of HS-CRP was available. On the basis of the local diagnostic threshold (i.e., 3.0 mg/L), elevated values of HS-CRP were observed in 43% of patients, more specifically in 32% of those with aura and in 55% of those without (p = 0.07).

Silva et al. carried out a cross-sectional study including 25 migraineur patients with aura (3 men and 22 women; mean age, 29 ± 7 years), 25 migraineur patients without aura (3 men and 22 women; 31 ± 7 years) and 25 non-pain controls (3 men and 22 women) [12], and observed that the levels of CRP did not significantly differ between controls (0.46 ± 0.36 mg/L) and migraineur patients with (0.44 ± 0.29 mg/L; p = ns) or without (0.66 ± 0.41 mg/L; p = ns) aura.

Vanmolkot and Hoon assessed the interticial concentration of CRP in 50 young adult patients with migraine (32 with and 18 without aura; 39 females and 11 males; mean age 24 ± 4 years) and 50 controls [13], and found that the median CRP level was significantly higher in patients with migraine [142 mg/L; interquartile range (IQR), 0.59–2.48 mg/L] than in controls (0.90 mg/L; IQR, 0.36–1.79 mg/L; p = 0.03). It is also noteworthy that, when compared with controls, CRP values were found to be higher in patients without aura (2.11 mg/L; IQR; 1.39–4.69 mg/L; p < 0.001), but not in those with aura (1.11 mg/L; IQR, 0.51–1.87 mg/L; p = ns).

Kurth et al. performed a large cross-sectional study on 27,626 women aged 45 years or older, 5087 (18.4%) of whom with migraine [14]. The concentration of CRP was found to be significantly higher in women with migraine than in those without (3.97 vs. 3.66 mg/L; p < 0.001). The CRP level was also higher in migraineur women without aura than in those with aura (4.08 vs. 3.86 mg/L; p = 0.003). A significant association was also found between elevated biomarker levels and migraine, with an OR of 1.13 (95% CI 1.05–1.22; p = 0.002).

Guldiken et al. studied 60 patients (46 females and 16 males; mean age 38 ± 10 years) with migraine and 25
Table 1  Synthesis of published studies that have investigated the clinical and epidemiological association between C-reactive protein (CRP) and migraine.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of study</th>
<th>Study population</th>
<th>Outcome</th>
<th>References</th>
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<tbody>
<tr>
<td>Welch et al., 2006</td>
<td>Retrospective</td>
<td>– 60 patients (54 females) with migraine</td>
<td>– High prevalence of elevated CRP values in patients without than in those with aura</td>
<td>[11]</td>
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<tr>
<td>Silva et al., 2007</td>
<td>Cross-sectional</td>
<td>– 50 patients (44 females) with migraine</td>
<td>– No significant differences of CRP values between cases and controls</td>
<td>[12]</td>
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<tr>
<td>Vanmolkot et al., 2007</td>
<td>Cross-sectional</td>
<td>– 50 patients (39 females) with migraine</td>
<td>– Higher CRP values in subjects with migraine without aura than in those with aura</td>
<td>[13]</td>
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<tr>
<td>Kurt et al., 2008</td>
<td>Cross-sectional</td>
<td>– 5087 women with migraine</td>
<td>– Higher CRP values in subjects with migraine without aura than in those with aura</td>
<td>[14]</td>
</tr>
<tr>
<td>Guldiken et al., 2008</td>
<td>Cross-sectional</td>
<td>– 60 patients (46 women) with migraine</td>
<td>– No significant differences of CRP values between cases and controls</td>
<td>[15]</td>
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<tr>
<td>Gudmundsson et al., 2009</td>
<td>Cross-sectional</td>
<td>– 598 patients (357 women) with migraine</td>
<td>– No significant differences of CRP values between cases and controls</td>
<td>[16]</td>
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<tr>
<td>Tietjen et al., 2009</td>
<td>Cross-sectional</td>
<td>– 125 women with migraine</td>
<td>– Higher CRP values in subjects with migraine without aura than in those with aura</td>
<td>[17]</td>
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<tr>
<td>Hamed et al., 2010</td>
<td>Cross-sectional</td>
<td>– 44 subjects with migraine</td>
<td>– Higher CRP values in subjects with migraine without aura than in those with aura</td>
<td>[18]</td>
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<tr>
<td>Nelson et al., 2010</td>
<td>Cross-sectional</td>
<td>– 2295 children or adolescents with migraine</td>
<td>– Higher CRP values in subjects with migraine without aura than in those with aura</td>
<td>[19]</td>
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<tr>
<td>Guldiken et al., 2011</td>
<td>Cross-sectional</td>
<td>– 50 patients with migraine</td>
<td>– No significant differences of CRP values between cases and controls</td>
<td>[20]</td>
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<tr>
<td>Yilmaz et al., 2011</td>
<td>Cross-sectional</td>
<td>– 62 patients (49 women) with migraine</td>
<td>– Rate of increased CRP values double in cases than in controls, but with no statistical significance</td>
<td>[21]</td>
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<tr>
<td>Theodoropoulos et al., 2011</td>
<td>Cross-sectional/</td>
<td>– 7 patients with migraine</td>
<td>– Higher CRP values in subjects with migraine without aura than in those with aura</td>
<td>[22]</td>
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<tr>
<td>Tietjen et al., 2012</td>
<td>Cross-sectional</td>
<td>– 125 women with migraine</td>
<td>– Adverse Childhood Experiences positively associated with CRP values</td>
<td>[23]</td>
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<tr>
<td>Meng et al., 2012</td>
<td>Interventional</td>
<td>– 43 patients with migraine</td>
<td>– Clinical improvement associated with decrease of CRP</td>
<td>[24]</td>
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<tr>
<td>Güzel et al., 2013</td>
<td>Cross-sectional</td>
<td>– 51 patients (36 women) with migraine</td>
<td>– Higher CRP values in subjects with migraine without aura than in those with aura</td>
<td>[25]</td>
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<tr>
<td>Rockett et al., 2013</td>
<td>Cross-sectional</td>
<td>– 30 women with migraine</td>
<td>– No significant differences of CRP values between groups</td>
<td>[26]</td>
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<tr>
<td>Fava et al., 2013</td>
<td>Cross-sectional</td>
<td>– 166 women with migraine</td>
<td>– No significant differences of CRP values between groups</td>
<td>[27]</td>
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men and women (615 males and 730 females; mean age 28±5 years) from the Reykjavik Study for the Young [16]. The prevalence of migraine in the entire study population was 8.2% (598/7251 cases; 411 in the Reykjavik Study and 187 in Reykjavik Study for the Young; 396 migraine with aura and 202 migraine without aura; 241 males and 357 females). Age- and multivariable-adjusted CRP values were not significantly different between migraineur males (0.79 mg/L; 95% CI 0.69–0.91 mg/L) and healthy men (0.83 mg/L; 95% CI 0.77–0.90 mg/L; p=0.44), as well as between migraineur females (0.87 mg/L; 95% CI 0.75–0.99 mg/L) and healthy women (0.87 mg/L; 95% CI 0.79–0.97 mg/L; p=0.90). No significant differences were also observed when CRP values of controls subjects were compared with those of migraineurs with or without aura (all p>0.05). Finally, the rate of subjects with CRP values >3.0 mg/L did not significantly differ among patient groups (i.e., healthy, migraineur patients with and without aura; p=0.43).

Tietjen et al. studied 125 women with migraine (61 with and 64 without aura; mean age 37±9 years), along with 50 female healthy controls [17]. The levels of CRP were found to be significantly higher in migraineur subjects (3.96±0.40 mg/L) than in controls (1.60±0.60; p=0.002), but were not significantly different in women with (4.56±0.58 mg/L) or without aura (3.38±0.56 mg/L; p=0.20).

Hamed et al. studied 44 patients with migraine (14 with aura, 24 without aura and 6 with transformed migraine; 5 men and 39 women; mean age 30±8 years) and 35 healthy controls (8 men and 27 women) [18]. The concentration of CRP was found to be lower in the control group (0.72±0.51 mg/L) that in migraineur patients with (0.92±0.50 mg/L; p=0.05) or without aura (0.95±0.47 mg/L; p=0.05), as well as in those with transformed migraine (1.10±0.36 mg/L; p=0.012). No significant differences were observed among the groups of patients with different forms of migraine (all p>0.05).

Nelson et al. carried out a very large cross-sectional study on 11,770 children or adolescents aged 4–19 years who were enrolled in the National Health and Nutrition Survey (NHANES) in 1999 through 2004, with an overall prevalence of frequent migraine of 19.5% (2295 cases) [19]. In this large population cohort, the concentration of CRP was found to be slightly but significantly higher in cases (1.9±0.1 mg/L) than in controls (1.5±0.1 mg/L; p<0.01). In fully adjusted multivariable regression analysis, CRP was a significant predictor of migraine (OR 1.23; 95% CI 1.00–1.51).

Guldiken studied 50 women with migraine (mean age 38±9 years) and 25 matched non-pain controls [20]. The concentration of HS-CRP was found to be slightly higher but not significantly different between cases (4.28±0.41 mg/L) and controls (3.91±0.89 mg/L; p=ns). No significant differences were also observed between migraineurs with (n=23; 4.06±3.98 mg/L) or without (n=27; 4.46±4.1 mg/L; p=ns) aura, nor between women with frequent (n=33; 4.40±3.72 mg/L) or seldom (n=17; 4.76±5.04 mg/L; p=ns) migraine attacks.

Yilmaz et al. performed a cross-sectional study including 62 patients with migraine (13 males and 49 females; mean age 34±9 years) and 50 healthy matched controls (10 men and 40 women) [21]. Although the rate of increased values of CRP (i.e., >3.1 mg/L) was neatly double in cases than in controls (23% vs. 10%), this difference did not achieve statistical significance (p=0.34).

Theodoropoulos et al. studied seven migraineur subjects aged 15–59 years, who were treated with allergenspecific sublingual immunotherapy [22]. At the time of enrolment, the concentration of CRP was significantly higher in these patients than in nine healthy, matched controls (2.1±1.0 vs. 0.8±0.3 mg/L; p=0.009). After 10–12 months of immunotherapy, symptoms of migraine significantly improved and the concentration of CRP decreased contextually (p=0.013).

Tietjen studied 125 women (age 18–50 years) with interictal migraine along with 50 healthy controls [23]. The score of the History of Adverse Childhood Experiences (ACEs), a specific questionnaire designed to assess health outcomes in adults, was significantly associated with HS-CRP (r=0.98; p<0.001). The level of HS-CRP was also a significant predictor of ACEs in multivariate regression analysis, exhibiting an OR of 4.05 (95% CI 1.56–10.51; p=0.02).

Meng et al. carried out an interventional study in 43 patients with migraine aimed to investigate the effects of pine needle moxibustion (21 cases) and medicated thread moxibustion of Zhuang medicine (22 cases) [24]. Both therapies were effective to improve the symptoms of disease, with complete remission rates observed in 48% and 14% of cases and effective rates of improvement in 91% and 50% of cases, respectively. Interestingly, the concentration of HS-CRP decreased significantly in both groups (from 4.3±1.0 to 2.1±0.9 mg/L and from 4.3±1.1 to 3.4±1.1 mg/L, respectively). The decrease of HS-CRP was significantly greater in the former group with the better outcome than in the latter (p<0.05).

Güzel et al. performed a cross-sectional study including 51 patients with migraine (27 with migraine with aura aged 37±3 years and 24 with migraine without aura aged 35±3 years; 15 men and 36 women) and 27 healthy controls (11 men and 16 women) [25], and found that the concentration of CRP was significantly lower in the
control population (3.5±1.6 mg/L) as compared with both migraineur patients with (15.6±7.2 mg/L; p<0.001) and without aura (11.2±2.8 mg/L; p<0.001). The concentration of CRP did not differ in patients with migraine with or without aura (p=0.28). Interestingly, receiver operating characteristic (ROC) curve analysis showed that CRP was a significant predictor of migraine (AUC 0.78; 95% CI 0.68–0.89; p<0.001).

Rockett et al. carried out a case-control study including 30 female migraineurs aged 18–55 years (15 obese and 15 normal weight) and 29 healthy controls (14 obese and 15 normal weight) [26]. The concentration of CRP was not found to be significantly different across the different groups by ANOVA (p=0.057). No difference was also found between normal weight women with and without migraine (4.0 mg/L, IQR 4.0–4.0 mg/L vs. 4.0 mg/L, IQR 4.0–4.0 mg/L; p=ns), as well as between obese women with or without migraine (4.0 mg/L, IQR 4.0–18.0 mg/L vs. 10.0 mg/L, IQR 4.0–12.0 mg/L; p=ns).

Finally, Fava et al. studied 166 Caucasian women aged 41±5 years with migraine (83 with episodic migraine and 83 with chronic migraine) along with 83 non-pain healthy controls [27]. The concentration of HS-CRP measured by an ELISA was found to be almost identical when comparing healthy controls (5.7±1.4 mg/L) to women with episodic (5.6±0.8 mg/L; p=0.023) and chronic (6.0±1.2 mg/L; p=0.56) migraine.

**Meta-analysis of published studies**

To evaluate the overall relationship between CRP and migraine in cross-sectional studies, we used a parametric analysis whenever possible (i.e., when the standard errors or variances and sample sizes were reported) to estimate the weighted mean difference nested in a random effect model, with corresponding p-values and 95% CI as specified elsewhere [28]. Heterogeneity across studies was also assessed by χ² based statistics and I-square test, where thresholds of 25%, 50% and 75% designate low, moderate, and high heterogeneity [29].

Interestingly, when all studies reporting sufficient data about CRP values were pooled (n=12; 6980 cases and 38,975 controls) [12–16, 18, 20, 25], CRP values remained significantly higher in both migraineur patients with aura (n=1939; weighted mean difference 0.88 mg/L; 95% CI 0.63–1.14 mg/L; p<0.001) or without aura (n=2483; weighted mean difference 1.04 mg/L; 95% CI 0.78–1.30 mg/L; p<0.001) when compared with controls (n=29,354).

Finally, the concentration of CRP in migraineur patients without aura was also slightly but significantly higher than that of migraineur patients with aura (weighted mean difference 0.13 mg/L; 95% CI 0.07–0.20 mg/L; p<0.001).

**Conclusions**

Migraine is a highly prevalent and frequently disabling condition, which poses a remarkable medical and economic burden on human society. With a worldwide estimated prevalence of approximately 15%, migraine is the third most common disease in both genders, behind dental caries and tension-type headache. It is also noteworthy that, only based on ictal disability, migraine is ranked seventh highest among specific causes of disability, being globally responsible for 2.9% of all years of life lost to disability (YLDs) [30]. These apprehensive figures have paved the way to an ever growing number of studies aimed to define biological associations and potential biomarkers that would help to reduce the prevalence of this condition by more efficient means of early diagnosis, prevention and therapy [31, 32].

It is now undeniable that neurogenic inflammation plays a crucial role in migraine [33]. The concept of sterile inflammation of cranial blood vessels during migraine attacks was firstly postulated by Moskowitz, exactly 30 years ago [34], and still represents the foundation of the current therapy based on triptans and non-steroidal anti-inflammatory drug (NSAIDs), which act through peripheral blockade of small fiber (C or A-delta)-dependent neurogenic inflammation within the dura [33].

Despite the wide inter-study heterogeneity which prompted us to use a random effect model for weighting the effect size, it is not surprising that our analysis of the current scientific literature provided reliable evidence of a potential epidemiological association between increased concentration of CRP and migraine, thus paving the way to further clinical investigations about anti-inflammatory agents that may contextually decrease the risk of cardiovascular disease and reduce the burden of migraine in the general population. Interestingly, Liberopoulos et al. first described the case of a 58-year-old man with peripheral...
arterial disease and hyperlipidemia, whose frequent attacks of migraine with aura completely disappeared after therapy with atorvastatin 20 mg/day [35]. Medeiros et al. also recently described the results of an open-label, prospective, parallel group, active comparator study of simvastatin versus propranolol for the prophylactic treatment of migraine in 54 women (aged 18–45 years) with more than six migraine attacks per month [36]. The responder rate in the simvastatin group was similar to that in the propranolol group (83% vs. 88%; p=0.71 by Fisher’s exact test), thus emphasizing the potential efficacy of statins for prevention of migraine. A phase II combined trial of simvastatin (20 mg bid) and vitamin D3 (1000 IU bid) therapy for prophylactic treatment of episodic migraine is also undergoing [37]. It is hence reasonable to imagine that, among their various pleiotropic properties, statins may also be effective to improve endothelial function and endothelium-dependent vasodilatation in cerebral arteries [38], thus preventing or counteracting the decrease of cerebral blood flow, which is the primary trigger of neurogenic inflammation [5].

As regards the potential biological association between migraine and CRP, it seems implausible to suggest that this biomarker may actively participate to the pathogenesis of migraine according to the current scientific evidence. It is hence more reasonable to hypothesize that increased values of CRP in migraineur patients would reflect underlying pathogenic mechanisms (e.g., hypertension, diabetes, dyslipidemia, obesity and depression) or pathological conditions (e.g., vascular inflammation and/or impaired vascular reactivity) that are shared by migraine and cardiovascular disease [39] or, to put it simple, may represent an epiphenomenon of neurogenic inflammation (Figure 1). This hypothesis is also supported by the two interventional studies which showed that the concentration of CRP decreased in association with improvement of migraine symptoms [22, 24].

Conflict of interest statement

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Giuseppe Lippi was born in Camposampiero (Padua, Italy) on October 4th, 1967. During the years spent at University, he started to work in the clinical laboratory of the Academic Hospital of Verona. He undertook his degree in Medicine in 1986 and specialized in Clinical Biochemistry and Laboratory Medicine in 1992. He has spent the first years after his degree (1993–1994) working in research at the Northwest Lipid Research Laboratories (Seattle, WA, USA), where he developed some immunochemical methods for assessment of plasma lipoproteins. He returned to the Academic Hospital of Verona in the period 1996–2009, where he served as an Associate Professor of Clinical Biochemistry and senior assistant in the laboratory of Clinical Chemistry and Hematology. During this period, he performed several studies in the field of atherosclerosis, namely on lipoprotein(a) and lipoprotein metabolism, development and validation of innovative biomarkers of cardiovascular disease and preanalytical variability. In 2009, he finally moved to Parma, where he currently serves as Director of the Clinical Chemistry and Hematology Laboratory of the Academic Hospital of Parma. His main activities also involve teaching and translational research in the field of laboratory medicine. As regards to scientific activity, he has published 985 scientific articles in peer-reviewed journals indexed in Medline and Scopus (more than 90% as first, second or last author), his total Impact Factor is 3340, his Mean Citations per Article is 9.3 and the Hirsch Index (H-index) is 49. He has participated to more than 500 national and international congresses and has given more than 150 presentations to national and international meetings. He is also Associate Editor of Clinical Chemistry and Laboratory Medicine and Seminars in Thrombosis and Hemostasis, peer-reviewer of most of the clinical chemistry and sports medicine journals, Chairman of the Scientific Division of Italian Society of Clinical Biochemistry and Molecular Biology (SiBiCo), Chief of the Italian Intersociety Study Group on the “Extra-analytical variability of laboratory testing”, Member of the European Scientific Advisory Board (ESAB) and of the EFLM working group on preanalytical variability.
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