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Long-Term Effects of Critical Care Insults on Lipoprotein Metabolism

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Abstract

Background: Several reports demonstrated acute changes in lipoprotein profiles during the acute phase of critical care illness (CCI), with significantly fewer investigations suggesting the persistence of lipid abnormalities past 28 days from onset of CCI, or into recovery. Theoretically, their persistence into a recovery of CCI may profoundly impact health as dyslipidemias are considered critically important in the natural history of atherosclerosis. Considering the increased incidence of survivorship after CCI (sepsis, trauma, severe surgery, burn), and the profound effect of even small changes in lipid makeup over time, investigating the persistence of lipid profile abnormalities addresses important health concerns. Here, we conducted a comprehensive review focusing on long-term (28 days or greater) lipoprotein abnormalities after CCI onset.

Methods: The supervised, narrative literature review utilized the PubMed, EBSCO, and Google Scholar databases using keywords (sepsis, trauma, surgery, stroke, recovery). In addition, we pursued studies focusing on 28 days observation periods, at minimum, after the resolution of acute inflammation. We identified 26 studies fitting our criteria, with another 11 included because of their input value.

Results: Only a handful of studies investigated long-term lipid profiles after sepsis, trauma, surgery, or traumatic brain injury. Persistent depression of HDL-c and LDL-c serum levels were the hallmarks of several post-CCI conditions. Furthermore, few investigators reported an increase in the oxidation of LDL. One animal study linked these observations to acceleration in the atherosclerotic process in animals surviving weeks after sepsis resolution.

Conclusions: Scant data indicates that recovery from critical care illness is associated with several persistent lipoprotein abnormalities. Numerous gaps in knowledge persist, particularly in terms of the clinical translation of observed lipid abnormalities into long-term cardiovascular outcomes post-CCI.

Keywords

LDL-c, HDL-c, VLDL-c, Oxidized LDL-c, Cholesterol, Sepsis, Trauma, Traumatic brain injury, Surgery, Cerebrovascular accident, Lipoprotein profile

Abbreviations

ACS: Acute Coronary Syndrome; AIS: Acute Ischemic Stroke; APACHE: Acute Physiology, Age, and Chronic Health Evaluation; ApoA-I: Apolipoprotein A-I; ApoB: Apoliprotein B; ASCVD: Atherosclerotic Cardiovascular Disease; CABG: Coronary Artery Bypass Grafting; CCI: Critical Care Illness; CETP; Cholesteryl Ester Transfer Protein; HDL-C: High Density Lipoprotein Cholesterol; ICU: Intensive Care Unit; LDL-C: Low Density Lipoprotein Cholesterol; MICU: Medical Intensive Care Unit; MOD: Multiple Organ Dysfunction; OxLDL: Oxidized Low Density Lipoprotein; PLTP: Phospholipoproteins Transfer Protein; MI: Myocardial Infarction; sdLDL: Small Dense Low Density Lipoprotein; SIRS: Severe Inflammatory Response Syndrome; SN1: Substitution Nucleophilic Unimolecular; STEMI: ST-Elevation Myocardial Infarction; TBI: Traumatic Brain Injury

Background

Among survivors of critical care illness (CCI), the acute inflammatory response determines the trajectory of recovery [1-4]. Interestingly, CCI survivors acquire new allostasis leading to alterations in homeostasis with unclear, long-term health consequences [5-8]. One of the features of newly emerged allostasis is immune system and metabolic re-programming. Considering the

essential role of the immune system and metabolome in responses to CCI and the progression of atherosclerosis, one could hypothesize that the immune system's atypical post-CCI performance may significantly impact the natural evolvement of atherosclerosis. Furthermore, acute illness is associated with changes in the lipoprotein profile during acute phase, endothelial injury and free radical environment. All of them may have an unfavorable effect on atherosclerosis progression setting the stage for long-term abnormalities during acute phase of illness [9,10]. Their persistence into recovery further increases the risk of atherosclerotic reactions. Noteworthy, even minor alterations in lipid metabolism affecting atherosclerotic plaque development have the potential to compound after years, especially if other processes accelerating atherosclerosis (diabetes, low grade inflammation) are already present [11].

Under nominal conditions, low-density lipoprotein cholesterol (LDL-c) plays an essential role in determining the progression of atherosclerosis. Significantly more pro-atherogenic forms such as oxidized LDL-c (oxLDL-c) are particularly prevalent in diabetes, obesity, and chronic inflammation [12,13]. Other pivotal processes contributing to atherosclerosis are endothelial dysfunction and infiltration of inflammatory leukocytes, which are both heavily driven by inflammation and oxidative stress [14]. All these conditions are prevalent during critical care illness and may persist afterwards, leading to accelerated atherosclerosis [15,16]. Furthermore, one needs to keep in mind that pre-existing lipoprotein profiles impact the progression of critical illness and set the stage for any atherosclerotic profile before CCI [17-20]. However, there is a gap of knowledge regarding the natural history of lipoprotein profile recovery long-term after CCI [21,22]. Considering the rapidly increasing population of sepsis survivors, the abnormalities of lipoproteins post-inflammatory states may provide insight into the long-term cardiovascular consequence of CCI [23].

The purpose of this review is to explore the effects of CCI on components of the lipoprotein profile during the recovery phase of these illnesses. We focused on sepsis, trauma, surgery, and traumatic brain injury due to their prevalence and high incidence of prolonged recovery among survivors [24-26]. We included literature on chronic liver failure considering the critical role of the liver in lipoprotein metabolism. Lastly, we investigated the recovery from cerebrovascular accidents and acute coronary syndrome because lipoproteins are particularly pivotal for the progression of these illnesses and the trajectory of both disease processes are frequently complicated by CCI. In both conditions, surgery is frequently implemented to correct pathological problem or address emerging complications. There is no uniform, pre-existing definition to differentiate acute and chronic changes in CCI, therefore, we decided to use the definition of greater or equal to 28 days as the landmark for post-CCI period. There are several manuscripts describing the abnormalities of lipoprotein metabolism during acute diseases, but we focused on the less explored, long-term aspects of dyslipidemias which are potentially more consequential for health maintenance [10,15,21,27]. We focused on situation where the pathological process has resolved so the chronic conditions (malaria, HIV, chronic hepatitis) were not included here. Considering significant differences in human and animal immunological mechanisms, we attempted to avoid animal studies when able. Due to the lack of data on this specific topic, some animal studies were included [28-30]. This review combines the limited long-term data with theoretical implications of investigations focusing on the short-term outcomes to provide a discussion frame. The novelty of this narrative review stems from its sole focus on the effects of common CCI on long-term aberrations in the lipoprotein profile with a particular emphasis on the acceleration of the atherosclerotic process.

Materials and Methods

This comprehensive review of the literature was completed utilizing the PubMed, EBSCO, and Google Scholar databases (Figure 1; Supplement #1). The following keywords, using MESH terms when possible, were utilized: Sepsis (C01.757), trauma injuries (Q000293), liver failure (C06.552.308.500), myocardial ischemia (C14.280.647), stroke (C10.228.140.300.775), surgery (C14.907.253.855), traumatic brain injury (C10.228.140.199.444, C10.900.300.087.235, C26.915.300.200.194), critical care (E02.760.190), postoperative care (E04.614.750), postoperative complication (C23.550.767), atherosclerosis (C14.907.137.126.307), lipoproteins (D10.532), survivors (M01.860), inflammation, critical care outcomes, treatment outcome, and long-term, identifying a total of 13,953 records. After removal of duplicates 12,726 records were identified. Only adult human investigations were included, except for a few animal studies where we had the ability to reach out directly to the investigators. The search criteria included full-text original studies (case report, journal article, clinical trials, clinical study, multicenter, and observational studies) which were written in English, have an abstract, and were published after 2000 with total of 9,946 records demonstrated. We screened the collected references resulting in the elimination of 9,981 articles due to the following reasons: 1) Irrelevance to the search objective, 2) The nature of the articles being case reports, and 3) System misclassification. A total of 55 full-text articles were closely evaluated, of which 29 articles were eliminated from this review for the following reasons: 1) Irrelevant study objectives, 2) Irrelevant results or

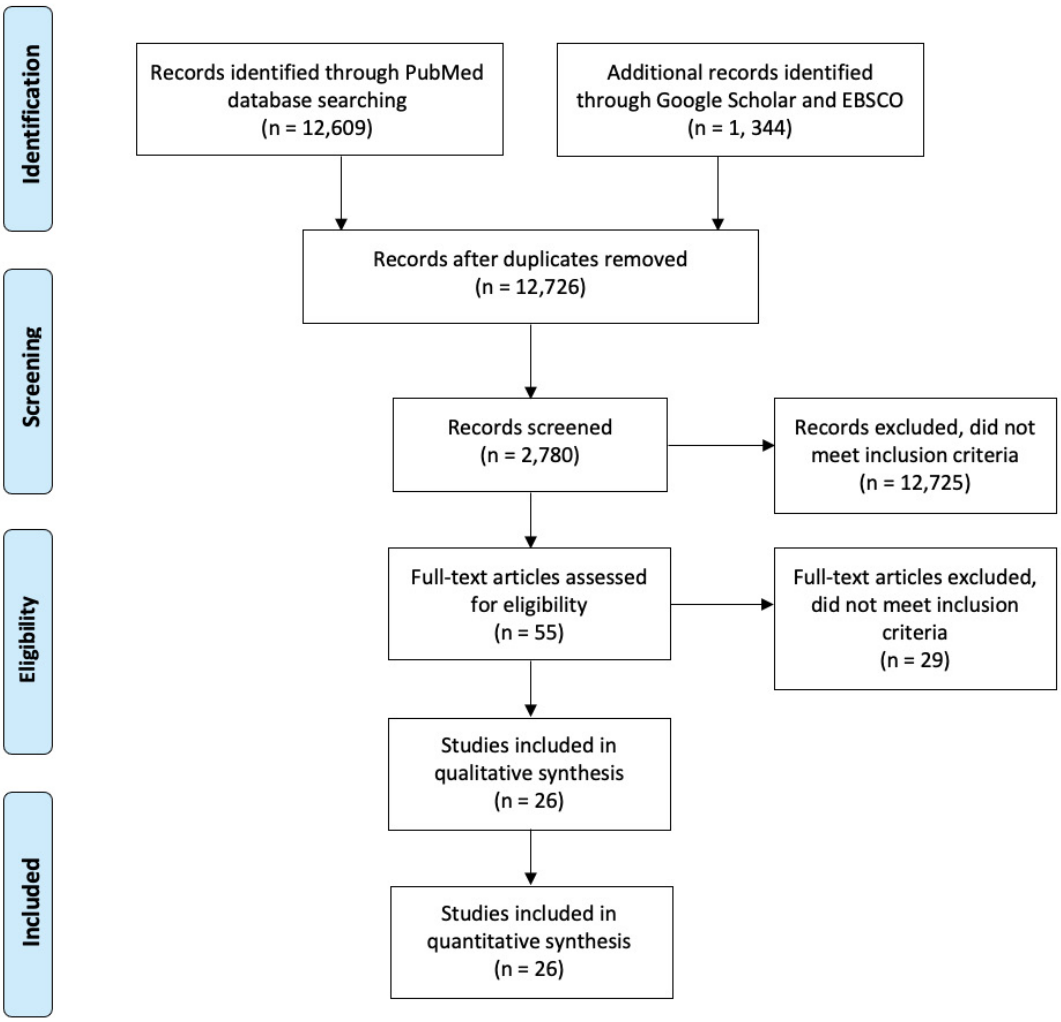

Figure 1: PRISMA Diagram: The literature included in this review was selected using the following criteria.

Table 1: Review of existing literature devoted to post-acute illness changes in critical care illnesses.

Ref#	Primary Author	Design	Sample (n)	Observational Period	Findings
[8]	Hacquebard, M.	Prospective Study	21	2 days	Decrease in LDL and but only moderate decrease in HDL
[14]	Hossain, E.	Experimental Study	> 10 × 104	Unknown	LPS enhances the cellular uptake of oxLDL in macrophages by upregulating LOX-1 through activation of ERK signaling pathway.
[16]	Kaynar, A. M	Prospective, Randomized Animal Study	78	N/A	Cecal ligation & puncture accelerates atheroma development (46% by 3 months, p = 0.03)
[17]	Kaysen G. A.	Retrospective Cohort Study	37,250	January 1, 2000 - December 31, 2012	Lipoproteins levels are inversely associated with infectious and all-cause mortality in the fully adjusted model (hazard ratio: 0.83; 95% CI: 0.75-0.91.)
[18]	Iribarren, C.	Cohort Study	120,571	1979-1993	Possible inverse association between the incidence of infections and total cholesterol.

[19]	Feng, Q.	Cohort Study	61,502	January 1, 1993 - December 31, 2017	The risk of sepsis and poor outcomes do not seem to be directly altered due to levels of LDL-C (r = 0.24; P < 2.2 × 10−16).
[20]	Chien, Y. - F.	Prospective Study	40	November 2006 - January 2009	Decrease serum HDL cholesterol levels may be a prognostic value in the first seven days (8.5 vs. - 17.4 mg/dL, P = 0.04).
[22]	Lee, S. H.	Retrospective Study	926	January 2007 - December 2015	Severe persistent hypocholesterolemia independently predicted in- hospital mortality (HR, 3.961; 95% CI).
[29]	Szeto, C. C.	Cross- Sectional Study	30	Unknown	Endotoxemia may have a role in a systemic inflammatory state and accelerated atherosclerosis in PD patients.
[31]	Fraunberger, P.	Letter to the Editor	--	N/A	Hypocholesterolemia could be linked with mortality in inflammation during critical illness.
[33]	Nishida, M.	Cross- Sectional Study	1078	2004	Components of MetS present profound effects on subclinical atherosclerosis in women rather than in men.
[32]	Al-Banna, N.	Review	--	N/A	OxLDL and LOX-1 are linked to proinflammatory disease mechanisms.
[34]	Lara- Guzman, O. J.	Experimental Study	35	Unknown	Induction biomarkers linked to oxidative stress and inflammation are triggered when THP-1 macrophages were treated with oxLDL (p < 0.001).
[29]	Wolfe, R. R.	Experimental Animal Study	11	N/A	The increase in triglyceride concentration in fasting dogs with gram-negative sepsis is the result of an increase in VLDL production (5-fold increase).
[35]	Tanaka, S.	Prospective Observational Study	40	Unknown	HDL levels are dramatically decreased in the acute phase of septic shock and there is a shift toward large HDL particles (r = 0.39, p = 0.012).
[31]	Lekkou, A.	Prospective Study	50	Unknown	Low cholesterol and lipoprotein concentrations are detected in septic patients, especially in individuals with poor outcome (HDL-C, p < 0.05).
[32]	Margarita de la Llera Moya	Randomized Controlled Trial	20	Unknown	Inflammation modulates human HDL composition (reduced HDL phospholipoproteins ~25%) and function in vivo.
[33]	Grion, C. M.	Prospective Cohort Study and Case- Control Analysis	1719	May 31st - December 1st, 2005	Each 1 mg dL (-1) increase in HDL decreased the odds of severe sepsis by 3% during hospitalization.
[34]	Wu, Q.	Retrospective Study	99	January 2017 - December 2017	The TG elevation that occurred during ICU stay was associated with worse outcomes and long- term hospitalization of the ICU.
[35]	Cirstea, M.	Blinded, Observational Cohort Study	200	January 2011 - June 2014	Plasma HDL-C level was the best prognostic marker for adverse outcomes in a suspected sepsis cohort (p = 0.469).
[36]	Larsen, S.F.	Prospective Cohort Study	2463	N/A	Increased incidence of cerebrovascular demonstrated by 3 patients.

[37]	Milone, M.	Observational, Comparative Cohort Study	160	Unknown	SG and MGB showed a similar efficacy in the improvement of lipoproteins profile of obese patients after 12-month follow-up (p = 0.039).
[39]	Genua, I.	Retrospective, Observational Study	185	January 2007-March 2015	The maximum increase in postoperative HDLc concentrations is observed 2 years after surgery (26.2% increase from baseline; p = 0.000).
[44]	Gordon, B. R.	Consecutive, Prospective Case Series	111	Unknown	Low cholesterol and lipoprotein concentrations found in critically ill surgical patients correlate with interleukin-6, soluble interleukin-2 receptor, and interleukin-10 concentrations and predict clinical outcomes (association between IL-6 and apolipoprotein A-I, p < 0.001).
[42]	Dunham, C. M.	Cohort Study	28	November 2000 - October 2002	Convalescing patients have improved cholesterol levels (143 ± 35), whereas dying patients appear to have progressive hypocholesterolemia (117 ± 27 mg/dl.)
[44]	Akan, A. A.	Experimental Animal Study	40	N/A	The spleen may have an important effect on lipoproteins metabolism and splenic auto transplantation may be protective in conditions with increased lipoproteins levels (HDL increased post-operatively, p < 0.05).
[45]	Li, Y.	Retrospective Matched Cohort Study	130	1990-2015	Splenectomy is associated with lower coronary artery atherosclerotic plaque severity (p = 0.03) and altered coronary artery macrophage distribution (p ≤ 0.0002).
[46]	Robinette, C. D.	Comparative Study	740	1939-1945	Risk of fatal infections is increased by asplenia; however, the risk of cancer was not increased.
[47]	Ferrante, A.	Retrospective Study	24	Unknown	Changes in proportion of regulatory T cells and monocytes may play a part in depressed mitogen responses of MNL from splenectomized subjects (P < 0.001).
[48]	Abbott, R. D.	Comparative Cohort Study	2425	1969-1971	Screening for total cholesterol alone in men and women aged 50 and older may not adequately identify the coronary candidate.
[49]	Kumar, P.	Prospective evaluation	60	N/A	Most patients had high LDL-C and low HDL-c levels within 24 hours of myocardial infarction.
[50]	Thakkar, H.	Case Control Study	260	Unknown	Acute Coronary Syndrome is associated with reduced HDL functions (p < 0.001).
[51]	Górecki, A.	Observational Clinical Study	348	Unknown	Higher levels of total cholesterol and LDL cholesterol during first 24 hours of acute myocardial infarction have a strong negative prognostic value.
[52]	Hacquebard, M.	Cohort Study	20	Unknown	Reduced α-toc level observed in the LDL fraction after cardiac surgery is due to the reduced circulating LDL particles (p < 0.0001).

[53]	Hlatky, M. A.	Comparative Cohort Study	23,353	January 2000 - December 2007	Patients who received CABG were less likely than patients who received PCI to fill prescriptions for secondary preventive medications and to use those medications consistently in the first year after the procedure ($p < 0.0001$).
[54]	Trieb, M.	Cross Sectional Study	59	Unknown	Liver disease alters cholesterol efflux capacity, paraoxonase activity, anti-inflammatory and endothelial regenerative activities of apoB-depleted serum.
[56]	Giovannini, I.	Prospective Study	92	N/A	Hypocholesterolemia in postoperative and critically ill patients is a cumulative index of severity of illness and has a relationship with poor prognosis ($p < 0.001$).
[57]	Zeljkovic, A.	Prospective Study	362	N/A	sdLDL is an independent predictor of both AIS onset ($p < 0.001$) and consecutive short-term mortality ($p < 0.05$).
[58]	Perovic, E.	Cohort Study	52	2011-2012	Early after the onset of acute ischemic stroke there is a marked change in the concentration of serum lipoproteins.
[59]	Wang, J.	Randomized Animal Study	15	N/A	Progression of atherosclerosis is accelerated following traumatic brain injury ($p < 0.05$).
[60]	Ahmadi, N.	Prospective Cohort Study	543	2007-2009	Mild traumatic brain injury is associated with the severity of coronary atherosclerosis.
[61]	Venetsanou, K.	Comparative Cohort Study	75	Unknown	LDL alone (lower, $p = 0.003$) or with IL-6 & IL-8 (higher, $p < 0.0001$) could be a prognostic factor of 30-day mortality for patients with traumatic brain injury.

outcomes, 3) Incorrect timing or stage of the disease, 4) Misclassification in type of article (case reports, case series report), and 5) Unpublished research methodology. A total of 26 original articles were included in this review. An additional 11 articles were included after following the leads from reviewed articles and suggestions during the review process. One manuscript denoting an animal study was included as well. Table 1 described the key human studies.

Results

Sepsis and other acute inflammatory conditions

Sepsis results in significant inflammation and immunological re-programming, potentially affecting the lipoprotein profile short- and long-term [1,6]. During an acute sepsis episode, the endothelium thickens while monocytes become inflammatory with frequent emergence of atypical, pro-atherogenic M2 type [28]. HDL-c and LDL-c levels were almost uniformly depressed proportionally to the severity of sepsis, while the oxidation of LDL-c (ox-LDL-c) was increased during the acute phase sepsis [21,29-36]. The serum VLDL-c level was increased during the acute illness, but it is unclear how long this effect persist [37]. The components of more advanced parts of the lipogram were not studied, with the exception for ApoA-1, which is depressed during the sepsis episode [30,31]. This data strongly suggests that sepsis could accelerate atherosclerosis due to the lost HDL-c protection, especially if this depletion change persists. Unfortunately, a robust body of evidence describing acute effects of sepsis is juxtaposed with the paucity of long-term data.

An animal study by Kaynar, et al. described an acceleration of atheroma formation in the aorta in five-month survivors of cecal ligation and puncture [38]. Confounders of the study included the involvement of only male animals deficient in apolipoprotein E [38]. Kaynar, et al. findings were consistent with the emergence of post-sepsis inflammatory syndrome, and is well established proof of post-sepsis atherosclerosis acceleration [1,6,8].

Van Leuvan, et al. demonstrated the suppression of HDL-c and LDL-c at four weeks after onset of sepsis in human survivors [39]. The decrease in HDL was accompanied by a modification in HDL composition with increased concertation of serum amyloid A during

recovery [39]. This alteration in HDL-c composition is linked to increased platelet levels and monocyte activation potentially accelerating atherosclerosis [11, 40]. In an independent investigation, Tanaka, et al. found a post-sepsis decrease in LDL-c, HDL-c and cholesterol 28 days post admission [41]. Similar data are seen in COVID-19 [42]. In all presented studies, the effect of sepsis on the acceleration of long-term lipid profiles was not the primary hypothesis. The scant data repetitively corroborate independently that even at 30 days post-sepsis, there are persistent, qualitative, and quantitative changes in the lipoprotein profile in survivors. However, long longitudinal studies are missing.

Surgery

The long-term effect of surgery on the lipid profile and natural evolution of atherosclerosis remains poorly described and almost impossible to distinguish from the effect of acute illness. In general, post-operative hypocholesteremia may persist over one year after surgery with unclear modification to the atherosclerosis progression [39, 43]. In emergent surgery, cholesterol levels were noted to decline immediately [22, 44]. The exception to this included neurological patients, where the level of HDL-c remains elevated, most likely secondary to the effect of phenytoin on HDL-c [45].

The clinical importance of these findings is obscure. Larsen, et al. suggested that accelerated atherosclerosis may be a reason for the increased prevalence of late cerebrovascular accidents after non-cardiac, non-carotid surgeries, however, most of the strokes occurred in the immediate post-operative period between days 5 and 26 [43]. It's important to note that this study was published in 1988 and the incidence of stroke was low (n = 6/2463). The increased incidence of embolic strokes was attributed to endothelial dysfunction rather than accelerated atherosclerosis [46].

Finally, we would like to note that bariatric surgery has been associated with a positive effect on the lipoprotein profile signified by an increase in HDL-c. This effect was inconsistent across studies and was believed to be due to the heterogeneity of the surgical technique used [47-49]. This net effect is most likely secondary to a change in dietary intake, not the persistent re-programming of the lipoprotein profile.

Trauma and splenectomy

Considering the fact that traumatic injuries have a higher prevalence within younger populations, abnormal changes within the lipid profile has the potential to have a more significant impact on long-term atherosclerosis. An acute decrease in lipoproteins after a traumatic injury is almost uniformly observed and linked to the degree of organ dysfunction [27].

There is a significant void in research involving long-term lipid profiles after a traumatic injury. We were able to locate three articles describing changes in the lipoprotein profile after a splenectomy. In most cases, splenectomy was the direct result of a traumatic injury, offering a natural, observational experiment in a very controlled way [50]. In general, data from human and animal studies demonstrated less atherosclerotic burden in the splenectomy patients. The long-term effects of a splenectomy induced the emergence of a pro-atherogenic lipoproteins that was at least partially diet related [51]. In particular, autopsies from 18 patients with a medical history spanning 20 years after a splenectomy demonstrate decreased macrophage density across all components of coronary arteries [52]. Concomitantly, an observational study of 740 United States service members subjected to splenectomies showed an excess in cardiovascular event incidence [53]. These results may suggest post-trauma changes in monocytes, may amplify rather lipoproteins abnormalities, as critical components of the atherosclerotic process [50]. The spleen is a critical partner in the modification of LDL particles and in monocyte turnover and activation [12,32,34,54].

ACS & Coronary Bypass Surgery

Despite numerous studies demonstrating the pivotal role of lipoprotein profile abnormalities in the development of atherosclerosis and the increased risk of acute coronary syndrome (ACS), little is known regarding how ACS as CCI affects the progress of atherosclerosis [9,10]. Acute changes in lipoproteins do not follow a "typical" pattern of change considering the fact that serum HDL-lipoprotein levels were not depressed during acute illness [55-57]. LDL-c was lower during acute ACS, but it is unclear how long these changes persisted [55-57]. This lipid profile predicted mortality acutely, but these findings are inconsistent with other studies demonstrating depression of LDL-c and HDL-c during acute phase of CCI [58].

We explored the effect of coronary artery bypass grafting (CABG) on the lipoprotein profile considering its correlation with ACS. In one study, 21 patients undergoing cardiac surgery with the application of cardiopulmonary bypass demonstrated a decrease in circulating LDL-c two days after insult, while HDL-c levels were somewhat less altered [59]. CABG was found to be related to a change in size of lipoproteins and a change in lipoprotein particle concentration. Other lipoprotein profile changes post-CABG included a decrease in total cholesterol levels by 35%, a decrease in triglycerides by 34.9%, and alteration in LDL as well as apoB [60]. These studies were the only two identified after the extensive literature search. Both studies focused on short-term outcomes. Despite the lack of extensive exploration

into lipoprotein changes post-CABG, they may offer a clue regarding physiological changes similar to CCI post-CABG. The effect of cardiac surgery on lipoprotein levels will be methodologically challenging. Most of these patients have a rich medical history including statin therapy [61]. They have myriad of pre-existing conditions interfering with atherosclerotic process. However, the importance of assessing CABG's long-term impact on lipogram may be critical in order to advocate for less invasive procedures, like percutaneous angioplasty. Interestingly, less invasive procedure demonstrated similar outcomes to CABG in case of intervention driven by cardiac atherosclerosis in the first place.

Stroke and traumatic brain injury

The contribution of cholesterol abnormalities to the emergence of acute stroke is well established. Similar to ACS, we do not know if stroke itself results in the acceleration of atherosclerosis *per se*. Patients who suffer a stroke demonstrate several abnormalities distinctive from those typically observed in CCI [29-31]. In a prospective study involving 110 participants with cerebrovascular event, blood samples were collected at five different time-points: On admission, 24 hours post-event, 48 hours post-event, 72 hours post-event, and at discharge [62]. Participants were noted to have an initial 23% decrease in HDL-c, LDL-c and total cholesterol levels. By hour 24 post-event, the lipoprotein levels increased, but then quickly began to decline by hour 48 until discharge. The authors also found that lower HDL levels at 48 hours were associated with higher incidences of 90-day mortality rates. Lower HDL levels at discharge were associated with higher amounts of disability. Lastly, the study demonstrated that patients with larger amounts of stroke volume had a higher serum level of LDL and total cholesterol as compared to other CCI. Varela, et al. examined lipid profiles in patients three months after cerebrovascular accidents (CVA). They determined a diminished anti-inflammatory potency of HDL-c [63]. These dynamics of HDL-c in the wake of the cerebrovascular event were like those observed in other CCI. However, increase in LDL-c is a unique observation for CVA patients, not noted in other study involving CCI patients.

Traumatic brain injury (TBI) resulted in changes in lipoprotein profile even when it presents as a sole insult. Animal data demonstrated an increase in atherosclerosis burden and macrophage retention within the plaque after TBI [64]. A different study recruited a total of 553 veterans who were followed over four years and noted an increase in plaque formation, which led to an increased risk of atherosclerotic events [65]. The study did not investigate the lipoprotein profile specifically while this and other studies suggested a myriad of factors affecting excessive atherosclerosis [10,15,37,66,67]. Indirect evidence linking both TBI and abnormal lipoproteins profile was demonstrated by the relationship between lipoproteins profile and cytokine profile resulted in excessive 28 days mortality in TBI victims [68]. However, this study did not venture for more than one month of observation and it is correlational in its nature.

Acute liver failure

The liver is critical for lipid metabolism and is frequently affected in CCI. Trieb, et al. (2016) demonstrated changes in lipoprotein profile among patients with acutely decompensated cirrhosis. Significantly decreased cholesterol levels were observed, including LDL-c, HDL-c, and apoA-I, and increased levels of C-reactive protein [69]. Even patients with relatively preserved liver function were noted to have diminished HDL-c and apoA-I levels. They linked depletion of apo-B to a decline in HDL-c and ultimately mortality on a sample of 59 patients. Even after the resolution of the liver injury, the lipoprotein profile continues to demonstrate abnormalities for a prolonged period of time. In a prospective study that involved a total of 93 patients who underwent hepatectomy due to liver malignancies or liver cirrhosis, acute reduction of cholesterol on a postoperative day one and three were observed [70]. The majority of the patients survived the surgery without complication and were noted to have a subsequent rebound of cholesterol on day seven. In non-survivors, cholesterol levels continued to decline until death. Again, this is consistent with prior observations [30,44,55].

Conclusion

In summary, this review demonstrated that almost any CCI induces short-term lipoprotein abnormalities [20,22,33,57,68,69,71]. This is consistent with a high prevalence of metabolic abnormalities at the cellular level and the role of the lipoprotein in response to acute infections. Decline in HDL-c into recovery was the commonest mark across multitude of CCI. Some investigators pointed to an increase in serum VLDL-c, LDL-c, and elevated oxidation of circulating lipoprotein molecules. If these changes persist, the natural evolution of atherosclerosis may be accelerated [1,5,8]. Theoretically, the almost uniform decline in HDL suggests the emergence of an unfavorable lipoprotein profile by itself, but it is often accompanied by a concomitant decline in LDL, the risk of accelerated atherosclerosis is even higher. LDL-hypolipoproteinemia may lower the risk of atherosclerosis but decline in HDL may tamper this deleterious effect. At the same time, an increased rate of lipoprotein modification may offset any theoretical benefit of lower LDL-c [34]. Lack of consistent studies hampers any definite conclusions.

The overall impression is that post-CCI lipid milieu

results most likely in a durable change in lipid profile extending to months after resolution of the acute illness process. No data for more than 6 months post-CCI lipid profile is present for any disease, which is one of the starkest findings of this manuscript. The data from animal studies strongly suggest long-term, deleterious effects on the lipogram and ultimately atherosclerosis in the aftermath of sepsis. Additional data from a patient suffering from long-term consequences of TBI and military staff after splenectomy further strengthen the case for the persistence of long-term lipid abnormalities [38,65,67]. However, the conclusion must be taken very carefully as the data from humans are somewhat opaque, showing variable to deleterious effects, and are correlational at best [20,29,51,57,59,60,65,66].

The persistence of unfavorable lipid profiles in patients after CCI suggests the therapeutic window to correct them in order to improve long-term outcomes. There are many agents to influence lipid profile, yet the question of whether prolonged post-septic abnormalities in the lipid profile can be effectively corrected with pharmacotherapy is not answered. Metabolic re-programming and the emergence of other pro-atherosclerotic conditions may hamper pharmacological interventions' benefit at reversing post-sepsis damage [72]. Due to the lack of adequate studies, this remains unknown.

One has to underline the critical difficulties in studying the presented topics. First, longitudinal studies are notoriously difficult to conduct. Second, the lipid profile is affected by diet and medications. The use of lipid-modifying drugs is common after stroke and ACS [61]. Third, the effects of CCI will be confounded by numerous variables, including the compliance with the therapy among the patients. Finally, atherosclerosis is a multifactorial disease. Besides lipid profiles, monocyte composition, monocyte activity, and overall endothelial function are critical and may independently alter the progression of atherosclerosis. All the reasons listed above stressed that we were forced to change the scope of our analysis. Our review was intended to be a systematic analysis from the onset of CCI. However, we quickly realized that there is not enough data to pursue our original methodology. Existing data is scarce and almost episodic for several patient populations with various endpoints, creating very high heterogeneity. This lack of well-grounded studies was surprising considering the increased interest in the health of the survivors. Furthermore, the advancements in medicine resulted in increased survivorship among the individuals coping with CCI. Considering the increased prevalence of survivorship and increased public interest, the lack of studies represents a significant knowledge gap that must be addressed. Lack of data limited the overall conclusion of this review to generalizations of few studies, indicating a knowledge gap that needs to be closed.

In summary, while few aspects of lipoprotein profile abnormalities have been studied in various critical care situations, there are significant gaps in knowledge evaluating the persistence and clinical importance of the long-term post-CCI lipid abnormalities. Additionally, future studies should assess the effects of lipoprotein profiles in the context of two main components of atherosclerosis progression: Monocytes and endothelium [1,8,10,73]. The current research suggests that CCI may have long-term effects on the lipoprotein profile; however, more definitive studies are needed considering the growing population of CCI survivors.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

KS: Manuscript preparation, proofing; JH: Literature review, manuscript preparation, proofing; CR: Literature research; DL: Literature research; JM: Keyword creation, concept, manuscript; MR: Manuscript preparation; UP: Literature search; KL: Concept, literature search, original manuscript, proofing.

Authors' statement

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