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Sickle Cell Trait and Exertional Collapse in Athletes: Risk, Mechanisms, and Screening Controversies - a narrative review

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Abstract

Background. Sick cell trait (SCT), the heterozygous carrier state for hemoglobin S, is generally considered benign but has been repeatedly implicated in exercise-related sudden death and exertional rhabdomyolysis in athletes and military recruits. The entity termed exercise collapse associated with sick cell trait (ECAST) remains incompletely understood, and its recognition, prevention, and screening have generated persistent controversy among hematology and sports medicine organizations.

Aim. To synthesise, from a clinically oriented and critical perspective, the epidemiology, proposed pathophysiology, clinical presentation, screening policies, and prevention strategies relevant to SCT-associated exertional collapse in athletic and military populations.

Materials and Methods. Narrative review of peer-reviewed English-language epidemiological studies, hospital and registry series, case reports, genetic and physiological investigations, and institutional guidance addressing SCT, exertional rhabdomyolysis, and exercise-related collapse.

Results. SCT carriers show a consistently elevated relative risk of exertional rhabdomyolysis and collapse across military and collegiate cohorts, though absolute risk remains low and mortality data are inconsistent. Proposed mechanisms include microvascular sickling under hypoxia/acidosis, altered lactate handling, hydration/thermoregulatory abnormalities, mitochondrial dysfunction, and

rare pathogenic variants. NCAA screening coincided with reduced sickling-related deaths in Division I football, but screening remains ethically contested, self-report underestimates true prevalence, and universal precautions are advocated as an alternative.

Conclusions. Current evidence supports individualized risk-stratified precautions, targeted education, and cautious, evidence-based screening rather than blanket policies, with substantial gaps remaining regarding causal mechanisms and optimal prevention.

Keywords: sickle cell trait; exertional rhabdomyolysis; exercise collapse; sudden death; athletes; genetic screening; hemoglobinopathy; heat illness

1. Introduction

Sickle cell trait (SCT) is the heterozygous carrier state resulting from inheritance of one normal β -globin allele and one sickle (HbS) allele, producing a hemoglobin profile in which HbS typically constitutes 30%-45% of total hemoglobin, with the remainder being normal HbA [1,2]. Unlike sickle cell disease (SCD), in which both β -globin alleles carry the sickle mutation and chronic hemolytic anemia, vaso-occlusion, and progressive multi-organ damage dominate the clinical picture, SCT has long been regarded as a largely benign carrier state, associated with normal life expectancy and generally normal hematological parameters [1,3]. It is estimated that approximately 300 million people worldwide carry SCT, with a prevalence of 6%-9% among African Americans in the United States and considerably higher rates in parts of sub-Saharan Africa, the Mediterranean basin, the Middle East, and the Indian subcontinent, reflecting the historical selective advantage conferred by the trait against *Plasmodium falciparum* malaria [2,4,5].

Despite this generally reassuring natural history, SCT has for decades been implicated as a risk factor for a specific and potentially catastrophic clinical presentation: sudden collapse and death occurring in the setting of extreme physical exertion, particularly in military recruits during basic training and in competitive athletes, most conspicuously American college football players, during intense conditioning sessions [2,5,6]. The clinical picture, now most often termed exercise collapse associated with sickle cell trait (ECAST), is characterized by a distinctive prodrome of muscle weakness and pain that is disproportionate to the exercise intensity, a "conscious collapse" without the altered mental status typical of exertional heat stroke, and, in fulminant cases, rapid progression to explosive rhabdomyolysis, hyperkalemia, cardiac arrhythmia, and death within a remarkably short interval [5,7,8]. The first cases were described in the 1970s among military recruits, and the

epidemiological signal was firmly established in 1987 by a landmark study of United States Army recruits that found a 27- to 32-fold higher risk of sudden unexplained death among Black recruits with SCT compared with those without the trait [2,5]. Subsequent work in collegiate athletics found the relative risk of exertional death in Division I football players with SCT to be increased approximately 37-fold compared with athletes without the trait, although the absolute risk remained low, on the order of 1 in 827 to 1 in a few thousand affected athletes over extended observation periods [2,9].

These striking relative-risk figures, combined with a series of highly publicized deaths in American collegiate football between 2000 and 2010, prompted the National Collegiate Athletic Association (NCAA) to introduce a mandatory sickle cell trait screening policy for Division I athletes in 2010, later extended to Divisions II and III [9-11]. The policy required documentation of SCT status through prior testing, a solubility test, or, in earlier iterations, a signed liability waiver declining testing [2,11]. This policy proved highly controversial. The American Society of Hematology (ASH), the Sickle Cell Disease Association of America (SCDAA), and other professional bodies have argued that current evidence does not justify mandatory genetic screening restricted to a specific population subgroup, that the intervention risks stigmatization and discrimination, and that universal precautions applied to all athletes regardless of SCT status would achieve comparable protective benefit without these harms [2,3,11]. Proponents of screening counter that documented knowledge of SCT status, combined with targeted education and individualized exercise modification, has been associated with a marked reduction in sickling-related fatalities in the years following implementation [9,10,12].

This debate is compounded by fundamental uncertainty regarding the underlying pathophysiology of ECAST. While intravascular sickling under conditions of hypoxia, acidosis, and dehydration provides an intuitive mechanistic narrative consistent with the biology of SCT, direct evidence linking postmortem sickling to the cause of death has been repeatedly challenged, since sickled erythrocytes are recognized as a common postmortem artifact unrelated to the antemortem cause of death [3,5]. Recent commentary has gone so far as to argue that "sickle cell crisis" is not a medically credible entity in SCT and should not appear on death certificates, attributing catastrophic exertional events instead to exertional rhabdomyolysis, sudden cardiac death, or other established mechanisms [3]. At the same time, emerging genetic and physiological research has identified candidate contributing factors beyond simple erythrocyte sickling, including variants in

genes governing solute transport and mitochondrial DNA maintenance, altered lactate kinetics, and impaired hydration and thermoregulatory responses in SCT carriers under exertional stress [13-16].

The purpose of this narrative review is to synthesize, from a clinically oriented and critical perspective, the epidemiology, proposed pathophysiological mechanisms, clinical presentation and differential diagnosis, screening policies, and prevention strategies relevant to SCT-associated exertional collapse in athletic and military populations. Rather than treating SCT as a uniformly hazardous condition, this review adopts a comparative stance, weighing epidemiological signal against absolute risk, contrasting mechanistic hypotheses, and foregrounding the genuine controversies—scientific, ethical, and clinical—that continue to shape practice in this field. The intention throughout is not merely to catalogue individual findings but to place them in explicit dialogue with one another: where military and collegiate athletic data diverge, where mechanistic hypotheses compete, and where methodological weaknesses limit the strength of causal inference, these tensions are foregrounded rather than smoothed over. Given the high population prevalence of SCT and the disproportionate concentration of research effort on a narrow set of settings—chiefly American collegiate football and United States military basic training—this review also aims to make explicit the substantial gaps in generalizability that limit extrapolation of existing findings to other sports, other geographic and health-system contexts, and to female athletes, who remain markedly underrepresented in this literature.

2. Materials and Methods

This article was conceived as a narrative review intended to provide a clinically oriented synthesis of the medical literature addressing sickle cell trait and exertional collapse in athletes, rather than a systematic review or meta-analysis; accordingly, no review protocol was registered, and no formal risk-of-bias appraisal or quantitative pooling of data was undertaken. The literature considered comprised peer-reviewed, predominantly English-language publications addressing sickle cell trait, exertional rhabdomyolysis, exercise collapse associated with sickle cell trait, and related sudden cardiac and exertional conditions in athletic and military populations, including epidemiological cohort studies, hospital and registry-based case series, individual case reports, genetic and physiological investigational studies, and consensus statements or position papers from relevant professional organizations. Sources were selected for their direct relevance to the clinical

and public-health questions surrounding SCT screening and exertional risk, and each digital object identifier was verified against its bibliographic registry entry prior to inclusion. Evidence was grouped thematically into sections addressing epidemiology and historical context; proposed pathophysiological mechanisms, including hematological, hemodynamic, metabolic, and genetic contributors; the clinical syndrome of ECAST and its differential diagnosis; sport- and setting-specific evidence, including American football, spin-class exercise, and military training; screening policy and its ethical and practical controversies; and prevention, management, and return-to-play considerations. Because source selection and thematic interpretation were, by design, narrative rather than systematic, this synthesis may be subject to selection and emphasis bias, and its conclusions should be read as a clinically reasoned overview rather than an exhaustive or formally graded account of all available evidence.

Where possible, findings from different study designs—large retrospective cohorts, registry-based surveillance analyses, small mechanistic physiological trials, genetic association studies, and single-patient case reports—were deliberately juxtaposed rather than presented sequentially, in order to make explicit both areas of convergence and areas of genuine disagreement. Particular attention was paid throughout to distinguishing statements supported by comparative, controlled, or population-based data from those resting primarily on case-level observation, and to noting explicitly where authors of the original studies themselves expressed methodological caution or ambivalence regarding causal attribution. This approach was chosen deliberately in preference to a simple sequential listing of "study X found... study Y found...", consistent with the intention of this review to function as a critical synthesis rather than a descriptive catalogue.

3. Sickle Cell Trait: Molecular Basis and General Epidemiology

SCT arises from a single point mutation in the β -globin gene (HBB) on chromosome 11, in which a GAG-to-GTG substitution replaces glutamic acid with valine at position six of the β -globin chain, producing hemoglobin S [4,5]. In the heterozygous state that defines SCT, one normal β -globin allele and one HbS allele are inherited, so that erythrocytes contain a mixture of HbA and HbS, typically with HbS representing 30%-45% of total hemoglobin, HbA the remainder, and small quantities of HbA₂ [1,2]. This is mechanistically distinct from homozygous SCD (HbSS) or compound heterozygous states such as HbSC or HbS β -thalassemia, in which HbS polymerization under deoxygenated conditions is far more extensive and clinically dominant [4,17]. Under normal

physiological oxygen tensions, SCT erythrocytes function essentially normally; polymerization of HbS into rigid, elongated fibers that distort the erythrocyte into the sickle shape requires substantially lower oxygen tensions or more pronounced acidosis than is typically encountered in resting tissue, which is the physiological basis for the trait's generally benign course [2,5].

Global prevalence estimates place the number of SCT carriers at approximately 300 million, with the United States National Committee for Quality Assurance and Centers for Disease Control and Prevention data indicating that roughly 6%-9% of African Americans carry the trait, corresponding to approximately 3 million individuals in the United States alone [1,3,5]. Prevalence is markedly lower in other ethnic groups, on the order of 0.2%-0.7% in Hispanic and Caucasian populations in some series, though the trait is also documented at meaningful frequency among people of Mediterranean, Middle Eastern, and Indian subcontinent ancestry, reflecting the historical geographic distribution of malaria endemicity [1,2]. In the specific context of American collegiate athletics, comparable prevalence figures have been reported: for example, one national survey found that among United States Army recruits, 7.8% of Black recruits carried SCT, closely mirroring general population estimates and suggesting no apparent selection bias against enlistment among trait carriers [2].

Historically, SCT has been considered largely asymptomatic, and indeed the overwhelming majority of carriers live full, unaffected lives, with normal longevity and no meaningful reduction in quality of life directly attributable to the trait [1,3]. Nonetheless, a body of literature—much of it originating from case reports, case series, and epidemiological studies in military and athletic settings—has documented an association between SCT and several uncommon but clinically important conditions: exertional rhabdomyolysis and exercise collapse, renal medullary carcinoma, painless or gross hematuria and renal papillary necrosis, splenic infarction at altitude, and a modestly increased risk of venous thromboembolism, particularly pulmonary embolism [1,18]. It is this cluster of exertion- and hypoxia-related complications, and in particular the phenomenon of sudden exercise-related collapse and death, that has generated the most sustained clinical and public-health attention, and which forms the central focus of this review.

The heterogeneity of the SCT carrier population deserves emphasis, since the overwhelming majority of published clinical and mechanistic research addresses individuals of West African ancestry, in whom the sickle mutation is thought to have arisen independently on several distinct

genetic haplotype backgrounds, each associated with somewhat different patterns of co-inherited genetic modifiers, including variable persistence of fetal hemoglobin and variable co-inheritance of alpha-thalassemia [4,17]. Co-inheritance of alpha-thalassemia, in particular, has been shown in physiological studies to modify hemorheological parameters in SCT carriers, and its variable presence across study populations represents a further, largely unaddressed source of heterogeneity that complicates direct comparison of mechanistic findings across different cohorts and geographic settings [15].

4. Historical Recognition and Epidemiology of Exertion-Related Death in SCT

The modern recognition of SCT as a risk factor for exertion-related sudden death traces to a series of military investigations beginning in the late 1960s. The earliest identified cases involved four United States Army recruits who died during or immediately after strenuous exercise during basic training at a moderate-altitude installation between 1968 and 1969; autopsy findings of diffuse intravascular sickling in these soldiers led investigators to conclude that a combination of altitude-related hypoxemia and intense exertion had precipitated fatal "sickle crisis" [5]. This case series, while limited in number, established the template for subsequent decades of clinical and epidemiological investigation, and it is notable, in retrospect, that the causal inference drawn from these initial cases rested entirely on postmortem histological findings whose interpretive validity has since been called into question, a methodological weakness that would recur throughout much of the subsequent literature in this field [3,5].

The landmark study establishing the epidemiological magnitude of the association was published in 1987, examining all deaths among active-duty United States military personnel between 1977 and 1981; this retrospective review concluded that the risk of sudden, unexplained death among Black recruits with SCT was approximately 30-fold higher than among Black recruits without the trait, and roughly 40-fold higher than among non-Black recruits generally [2,5]. The majority of these deaths occurred during the first month of training and were temporally associated with exertional activities requiring maximal effort, most commonly attributed at the time to exertional heat illness or exertional rhabdomyolysis [5]. Notably, a subsequent ten-year intervention study conducted by the same investigative group, in which Army drill sergeants actively monitored wet-bulb globe temperature and modified exercise intensity, rest cycles, and hydration protocols in response to environmental heat stress, appeared to eliminate or substantially reduce the excess

mortality previously associated with SCT during basic training, leading the Army to discontinue mandatory sickle cell gene screening in 1996 in favor of universal precautions applied to all recruits [5]. This early natural experiment is of considerable importance for the subsequent screening debate, since it demonstrated, decades before the NCAA policy was implemented, that environmental and exertional risk mitigation applied universally—without reliance on individual genetic knowledge—could apparently neutralize much of the excess mortality signal originally attributed to SCT.

In the civilian athletic domain, the first documented case attributed to sickling occurred in 1974, involving a 19-year-old American college football player who collapsed during conditioning workouts and subsequently died [5]. Between 1974 and 2010, an estimated 18 sickling-related deaths were reported in the lay press among American collegiate football players, with 11 such deaths occurring between 1999 and 2010 [5]. A pivotal epidemiological study reviewing all National Collegiate Athletic Association student-athlete deaths from January 2004 through December 2008 identified 273 total deaths across nearly 2 million athlete-participation-years; five of these deaths were specifically associated with SCT, all occurring during physical exertion and all in Black Division I American football players, yielding a relative risk of exertional death of approximately 37-fold in football players with SCT compared with those without the trait, corresponding to an absolute risk on the order of 1 in 827 affected athletes [2,5].

A subsequent and more granular epidemiological analysis, drawing on the National Registry of Catastrophic Sports Injuries over a twenty-year period from 1998 through 2018, quantified 187 non-traumatic fatalities in high school and college football players, of which 22 (12.1%) were attributed to exercise collapse associated with SCT (ES with SCT), behind sudden cardiac arrest (57.7%) and exertional heat stroke (23.6%) as causes of non-traumatic death [9]. This analysis is particularly informative because it directly evaluated the effectiveness of the 2010 NCAA SCT screening bylaw: the risk of an ES-with-SCT fatality in NCAA Division I athletes was found to be significantly lower after implementation of the bylaw (odds ratio 0.12, 95% confidence interval 0.02-0.95), with the average annual rate of Division I fatalities declining from 0.83 to 0.13 per year, an 85% reduction, and the incidence declining from 3.34 to 0.40 per 100,000 athletes, an 88% reduction [9]. By contrast, at the high school level, where no comparable mandatory SCT screening policy exists, the risk of an ES-with-SCT fatality was found to be 3.5-fold higher after 2010 than before (95% confidence interval 0.8-16.3, not reaching conventional statistical significance), with

the average annual incidence rising from 0.02 to 0.07 per 100,000 participants [9]. A companion analysis from the same research group similarly reported a 58% decline in the average annual number of SCT-related deaths in collegiate football following the 2010 policy, contrasted with a 400% increase in SCT fatalities at the high school level over the same interval [12].

These figures require careful interpretation. First, the absolute number of events remains small in every dataset—single digits to low tens of cases over decades of observation—so that percentage changes, however dramatic, are calculated on a fragile numerical base and are vulnerable to substantial statistical imprecision, as reflected in the wide confidence intervals reported [9]. Second, temporal trends in screening policy are confounded by simultaneous secular changes in heat-illness prevention, athletic training practices, and general medical awareness, making causal attribution to the screening policy alone difficult to establish with confidence [9,10]. Third, and most fundamentally, a large-scale United States Army study of 47,944 Black soldiers tested for hemoglobin AS status, discussed in detail in the following section, found that SCT was associated with a significantly higher risk of exertional rhabdomyolysis (hazard ratio 1.54, 95% confidence interval 1.12-2.12) but was not associated with a significantly higher risk of death from any cause (hazard ratio 0.99, 95% confidence interval 0.46-2.13), a finding that stands in direct tension with the football-specific mortality data and underscores genuine scientific disagreement regarding the mortality risk conferred by SCT once modern universal exertional-injury precautions are in place [19]. Table 1 summarizes representative epidemiological findings across military and collegiate athletic settings, illustrating both the consistency of the signal for exertional rhabdomyolysis and the greater heterogeneity of findings regarding mortality.

An important, and often underappreciated, methodological consideration in interpreting these divergent datasets is the substantial difference in surveillance methodology between the military and collegiate literatures. The Army cohort study benefited from prospective identification of all soldiers with documented hemoglobin AS status followed systematically over a defined multi-year interval, with cause-specific outcomes captured through standardized medical surveillance systems, whereas the football-specific fatality literature relies substantially on retrospective identification of fatal cases through registry review, media reporting, and after-the-fact determination of SCT status, frequently established only postmortem [9,12,19]. This asymmetry in surveillance rigor means that the two literatures are not, strictly speaking, measuring comparable underlying populations or comparable degrees of case ascertainment completeness, and this

asymmetry alone could plausibly account for at least part of the observed divergence in mortality risk estimates, independent of any true underlying difference in the physiological demands of military basic training versus football conditioning.

Table 1. Representative epidemiological studies of sickle cell trait, exertional rhabdomyolysis, and exercise-related death in military and athletic populations.

Source [ref]	Population / Design	Key finding regarding SCT
Kark et al., cited in [2,5]	US Army recruits, 1977-1981, retrospective review of deaths	Sudden unexplained death ~30- to 40-fold higher in Black recruits with SCT vs. without
Nelson et al. [19]	47,944 Black US Army soldiers, 2011-2014, Cox proportional-hazards cohort study	Exertional rhabdomyolysis HR 1.54 (95% CI 1.12-2.12); death from any cause HR 0.99 (95% CI 0.46-2.13), not significant
Harmon et al., cited in [2,5]	NCAA student-athletes, 2004-2008, ~2 million athlete-years	Relative risk of exertional death ~37-fold higher in Division I football players with SCT; absolute risk ~1:827
Boden et al. [9]	National Registry of Catastrophic Sports Injuries, HS/college football, 1998-2018	22/187 (12.1%) non-traumatic fatalities attributed to ES with SCT; risk in NCAA DI fell 85%-88% after 2010 screening bylaw; HS risk rose 3.5-fold (not significant)
Boden et al. [12]	Same registry, 20-year retrospective	Average annual DI SCT-related deaths declined 58% post-bylaw; HS SCT-related deaths increased 400%

Wang et al. [13]	20 NCAA Division I football players (10 SCT, 10 controls), longitudinal, 2 seasons	No deaths or serious clinical events; SCT players showed altered hematological and hydration markers over a full season
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5. Proposed Pathophysiological Mechanisms: Erythrocyte Sickling, Hypoxia, and Acidosis

The dominant mechanistic hypothesis for exertion-related collapse in SCT centers on the biophysics of hemoglobin S polymerization. Under conditions of reduced oxygen tension, HbS molecules undergo conformational change and aggregate into long, rigid polymers that distort the erythrocyte membrane, producing the characteristic sickle shape, reduced deformability, and markedly shortened erythrocyte lifespan [5,17]. In vitro studies have demonstrated that erythrocytes from SCT carriers can be induced to sickle within minutes under sufficiently low oxygen tension, and studies of venous blood drawn from the exercising limb of SCT individuals during arm-cranking exercise have documented measurable intravascular sickling occurring within minutes of intense effort [5]. The proposed sequence of events during extreme exertion involves a combination of local muscle hypoxia (as oxygen extraction outpaces delivery in maximally working muscle), systemic and local acidosis (from anaerobic glycolysis and lactate accumulation), and dehydration-related hyperosmolality and increased blood viscosity, all of which are known in vitro to promote and accelerate HbS polymerization [2,5,7].

This polymerization is hypothesized to precipitate microvascular occlusion, particularly within the already hypoxic, hyperosmolar, and acidotic environment of the renal medulla and within intensely working skeletal muscle, leading to localized ischemia, muscle necrosis, and, in severe cases, fulminant rhabdomyolysis with release of myoglobin, potassium, and other intracellular contents into the systemic circulation [5,7]. The clinical consequences of this cascade—hyperkalemia-induced cardiac arrhythmia, myoglobin-mediated acute kidney injury, and disseminated intravascular coagulation—provide a coherent, if largely inferential, explanation for the rapid progression from muscle weakness and pain to collapse and death that characterizes reported fatal cases [5,7,8]. It is worth emphasizing the specific vulnerability of the renal medulla in this proposed mechanism: this region of the kidney is physiologically characterized by relative hypoxia, high osmolality, and a low pH microenvironment even under normal resting conditions, owing to the countercurrent multiplication system responsible for urinary concentration, and these baseline

conditions are precisely those known to promote HbS polymerization in vitro, providing a biologically coherent explanation for the disproportionate representation of renal complications—hematuria, papillary necrosis, and renal medullary carcinoma—among the recognized clinical manifestations of SCT even outside the specific context of exertional collapse [1,5].

However, this mechanistic narrative, while biologically plausible, rests on a surprisingly thin evidentiary base when subjected to critical scrutiny. A fundamental methodological problem is that sickled erythrocytes are a well-recognized artifact of postmortem hypoxia and acidosis, occurring in the tissues of essentially all SCT carriers after death regardless of the actual cause of death, which makes histological identification of sickling at autopsy an unreliable indicator of antemortem pathophysiological causation [3,5]. This concern was raised explicitly and forcefully in a recent commentary from hematology experts, who reviewed the medicolegal history of this issue, including a striking account of expert testimony in a 1970s case in which a coroner attributed a custodial death to "sickle cell crisis" based solely on postmortem intravascular sickling, testimony that was successfully challenged on the grounds that such sickling is an expected postmortem finding with no established pathological significance [3]. The same commentary reports that a systematic review convened by the American Society of Hematology, after screening 1,474 citations, found no studies directly comparing uncomplicated acute pain crises in SCT to those in SCD, and concluded that because sickle cell crisis is not a recognized clinical entity in SCT, there is no valid evidentiary basis for attributing death in SCT carriers to a sickle cell crisis mechanism [3]. This position stands in direct opposition to the mechanistic assumptions underlying much of the earlier military and athletic literature and represents one of the central unresolved controversies in the field.

It is instructive to consider how these two positions—the traditional sickling-centered mechanistic narrative and the more skeptical, evidence-based reappraisal—might, in fact, be reconciled rather than viewed as strictly incompatible. It is entirely possible that microvascular sickling does occur, and does contribute mechanistically, in at least some fraction of ECAST cases, while simultaneously being true that postmortem histological identification of sickling cannot, on its own, distinguish those true causal cases from the far larger number of instances in which sickling is present as an incidental postmortem artifact unrelated to the actual mechanism of death. Under this reconciling view, the central scientific problem is not necessarily that sickling never contributes to exertional collapse, but rather that the field has historically lacked a reliable antemortem or

perimortem diagnostic method capable of distinguishing causally relevant sickling from incidental postmortem sickling, a methodological gap that persists to the present day and that substantially limits confidence in any single case attribution, however clinically suggestive [3,5].

6. Hemorheological and Vascular Contributions

Beyond simple erythrocyte sickling, a body of physiological research has examined broader hemorheological abnormalities in SCT carriers that might contribute to exertional risk independent of overt sickling. SCT carriers have been shown to exhibit increased blood viscosity, reduced erythrocyte deformability, and heightened vascular cell adhesion during and after intensive exercise compared with non-carrier controls, changes that are most pronounced during high-intensity training and the subsequent recovery period [1]. These rheological abnormalities are proposed to increase the risk of microcirculatory disturbance independent of frank polymerization, and have been suggested as a contributing mechanism to the excess risk of exercise-related sudden death observed epidemiologically [1].

Complementing these rheological findings, investigations of nitric oxide bioavailability and blood viscosity have suggested that elevated blood viscosity should itself be regarded as an independent risk factor for exercise-related sudden death in SCT carriers, operating through impaired microvascular flow and endothelial shear stress abnormalities that are exacerbated by the physiological stresses of exercise, including acidosis, dehydration, heat stress, and regional hypoxemia [13]. A study of NCAA Division I American football players with SCT, tracked longitudinally across two full competitive seasons and compared against position-matched controls without the trait, found that SCT athletes exhibited persistently greater red cell distribution width, a marker reflecting anisocytosis and morphological heterogeneity consistent with underlying red cell membrane stress, along with higher serum uric acid concentrations throughout the season and greater serum creatine phosphokinase concentrations at the pre-season baseline [13]. Interestingly, the same study found that SCT players demonstrated an improved fluid balance profile during preseason training camp relative to controls, with lower pre- and post-practice urine specific gravity and lower urine electrolyte concentrations but higher sweat sodium, potassium, and chloride concentrations, suggesting a compensatory shift toward greater renal and sweat electrolyte handling that may partly reflect targeted educational efforts regarding hydration in this population [13]. No serious adverse events, including no cases of rhabdomyolysis, were recorded in either

group across the two seasons of observation, a reassuring finding given the intensity of the training exposure, though the modest sample size (ten SCT athletes and ten controls) limits the statistical power to detect rare catastrophic events [13].

This finding regarding sweat electrolyte composition deserves further comment, since it bears directly on the practical hydration counselling given to SCT-positive athletes. If SCT carriers systematically lose more sodium, potassium, and chloride in sweat relative to non-carriers under matched training conditions, standard hydration guidance emphasizing plain water replacement alone might, at least in theory, be insufficient to prevent electrolyte derangement in this population during prolonged, heavy-sweating training sessions, and could plausibly warrant closer attention to electrolyte-containing fluid replacement specifically in SCT-positive athletes undertaking intensive preseason conditioning in hot environments [13]. However, given the very small sample size of this single study, this remains a hypothesis-generating observation rather than an established basis for differential electrolyte replacement recommendations, and no subsequent larger study confirming or refuting this pattern was identified in the literature reviewed here.

7. Lactate Metabolism and Metabolic Adaptations

A particularly instructive and somewhat paradoxical line of physiological investigation concerns lactate handling during high-intensity exercise in SCT carriers. Based on the lower index of oxygen supply to tissues and depressed muscle oxidative potential previously documented in SCT carriers, it was hypothesized that these individuals would demonstrate a higher reliance on non-oxidative glycolysis and, consequently, greater blood and muscle lactate accumulation during intense exercise, potentially compounding the acidosis thought to drive sickling [15]. A controlled physiological study comparing thirty adult male Cameroonian SCT carriers and healthy controls, with and without co-existing alpha-thalassemia, performing a standardized two-minute high-intensity cycling exercise, found the opposite: SCT carriers exhibited significantly lower blood lactate concentrations at exercise completion (7.08 mmol/L versus 8.59 mmol/L in controls, $p = 0.011$) and significantly lower muscle lactate concentrations measured directly by biopsy (113 mmol/kg dry mass versus 132 mmol/kg dry mass, $p = 0.022$) [15].

This counterintuitive finding was accompanied by a higher muscle content of the lactate/H⁺ transporter MCT4, involved in lactate and proton extrusion from myocytes, and a lower muscle content of β 2-adrenergic receptor, potentially reflecting reduced catecholamine-driven activation

of glycogenolysis and glycolysis during exercise [15]. During the subsequent recovery period, SCT carriers also demonstrated a significantly higher lactate removal rate constant, reflected in more rapid normalization of blood lactate and an earlier crossover point between glucose and lactate concentration curves, consistent with enhanced hepatic gluconeogenic uptake of lactate [15]. The authors of this study proposed that these findings, rather than representing pathology, may constitute a protective physiological adaptation that limits blood and tissue acidification during and after exercise, potentially explaining why catastrophic complications remain relatively rare given the high population prevalence of SCT, and additionally offering a plausible physiological explanation for the disproportionate representation of SCT carriers among elite short-distance sprinters [15]. This finding illustrates the genuine complexity of SCT exercise physiology and cautions against a simplistic narrative in which every physiological difference in SCT carriers is assumed to be maladaptive or risk-conferring.

The apparent contradiction between this metabolic study, suggesting a protective adaptation limiting acidosis, and the epidemiological literature documenting excess risk of collapse under extreme exertion, is worth dwelling on further, since it exemplifies a broader interpretive tension running through this entire field. One possible reconciliation is that the specific two-minute cycling protocol used in the lactate study, while intense, may not adequately model the qualitatively different physiological stress of prolonged, repeated maximal-effort sprint intervals under conditions of heat stress and progressive dehydration that are characteristic of the football conditioning sessions implicated in most fatal ECAST cases; it is conceivable that the protective lactate-handling adaptation observed under a brief, single bout of high-intensity exercise may be overwhelmed, or may even reverse, under the qualitatively different and more sustained metabolic and thermal demands of the training sessions actually implicated in fatal collapse [9,12,15]. This possibility, however, remains speculative, since no study identified in the literature reviewed here has directly measured lactate kinetics in SCT carriers under conditions closely replicating the specific serial maximal-sprint conditioning protocols associated with fatal collapse, representing a clear and specific gap for future physiological investigation.

8. Genetic Modifiers and Molecular Susceptibility Factors

Given that the overwhelming majority of SCT carriers tolerate even extreme exertion without incident, a persistent question has been whether additional genetic factors, beyond the HbS

mutation itself, modify individual susceptibility to exertional rhabdomyolysis and collapse. A genome-wide association study using whole-genome sequencing in a cohort of 23 SCT-positive African American cases with a documented history of exertional rhabdomyolysis and 53 SCT-positive controls without such history, supplemented with additional control genomes of African ancestry drawn from the 1000 Genomes Project, identified a non-synonymous variant (rs115958260, c.T1429C:p.C477R) in the SLC44A3 gene as significantly associated with exertional rhabdomyolysis at genome-wide significance in both single-nucleotide-polymorphism-based and gene-based association analyses [14]. SLC44A3 encodes a choline-like transporter with documented high protein expression in both skeletal muscle and kidney tissue, organs that are characteristically damaged in exertional rhabdomyolysis, and gene-set enrichment analysis further implicated solute-carrier-mediated transmembrane transport pathways more broadly [14]. This study's authors were careful to note the substantial limitations of the approach, including a small sample size that limited power to detect rare variants and the impossibility of fully excluding "false negative" control classification, since some control participants may simply never have been exposed to sufficiently extreme exertion to manifest a susceptibility [14].

Clinically characterizing the same cohort, the ERM cases in this study were predominantly male (86.7%), with a mean age of 33.8 years, and were significantly more likely to engage in high levels of strenuous physical activity than controls, consistent with the active-duty military status of most cases [14]. Clinically, the cohort exhibited a mean peak creatine kinase of 50,480 IU/L (range 989-400,000 IU/L), with severe muscle pain reported in 88.9% of episodes, weakness or fatigue in 60%, and exertional collapse specifically reported in 53.3% of cases, alongside acute kidney injury in 13.3% and compartment syndrome in 16.7% [14]. Recurrent episodes, defined as two or more distinct events, occurred in 39% of cases, indicating that for a substantial minority, susceptibility to exertional rhabdomyolysis is not a single unfortunate occurrence but a recurring predisposition [14].

A separate case-report investigation identified pathogenic heterozygous variants in genes governing mitochondrial DNA maintenance—POLG (p.Gly848Ser) and RRM2B (p.Met282Ile)—in two independent Black Service Members with documented episodes of exercise collapse associated with sickle cell trait (ECAST), both genes being established causes of mitochondrial DNA depletion syndromes characterized by impaired mitochondrial genome replication and consequent energy production deficits, particularly in skeletal muscle [16]. Direct functional

assessment of mitochondrial oxygen consumption in peripheral blood mononuclear cells from these two ECAST cases, compared against two SCT-positive controls without a history of collapse, demonstrated markedly lower reserve capacity, lower ATP-linked oxygen consumption, and a lower calculated "mitochondrial resilience index" (2.65 and 2.49 in the two cases, versus 4.43 and 5.17 in the two controls), providing direct functional evidence of impaired mitochondrial bioenergetic capacity in these ECAST cases [16]. While limited to two case-control pairs and therefore hypothesis-generating rather than definitive, this work is notable for directly linking a specific, biologically plausible molecular mechanism—energy production failure under exertional metabolic demand—to the clinical phenotype of ECAST in genetically confirmed SCT carriers [16].

The conceptual attraction of this mitochondrial hypothesis lies in its capacity to explain, at least partially, why the excess risk associated with SCT is confined to a small minority of carriers rather than manifesting broadly across the entire carrier population: if a second, independently segregating pathogenic variant affecting mitochondrial energy production is required to produce clinically significant susceptibility, the combined probability of inheriting both SCT and a rare mitochondrial DNA maintenance gene mutation would be expected to be considerably lower than the prevalence of SCT alone, consistent with the observed rarity of catastrophic collapse relative to the very high population prevalence of the trait itself [14,16]. This "two-hit" conceptual model, while attractive, remains unproven at a population level, since it has been demonstrated so far only in a small number of index cases rather than through systematic screening of a broader population of SCT carriers with and without a history of exertional collapse.

Complementing these genetic findings, transcriptomic profiling of skeletal muscle biopsies obtained at least six months after the most recent episode from nineteen patients with a documented history of exertional rhabdomyolysis, compared against eight healthy controls, revealed significant downregulation of genes involved in mitochondrial oxidative phosphorylation and the aerobic electron transport chain, alongside upregulation of genes involved in extracellular matrix structural organization and cell adhesion [20]. Although this cohort was not restricted to SCT carriers, and indeed did not report the SCT status of the controls, the pattern of findings—suppressed mitochondrial energy-production pathways alongside enhanced tissue-remodeling and repair pathways—was interpreted by the authors as evidence of an ongoing, months-long process of muscle tissue restoration following an episode of rhabdomyolysis, and was noted to parallel,

though not fully replicate, comparable transcriptomic signatures previously described in equine models of recurrent exertional rhabdomyolysis [20]. It is worth noting that this study's clinical cohort was drawn substantially from patients referred for evaluation of malignant hyperthermia susceptibility via caffeine-halothane contracture testing, a population that may not be directly generalizable to SCT-specific ECAST, though it nonetheless illustrates the broader molecular landscape of muscle recovery after exertional rhabdomyolysis regardless of the precipitating genetic or hematological background [20]. The persistence of a detectable transcriptomic signature at a minimum of six months post-episode is itself a clinically important finding, as it raises the possibility that skeletal muscle in individuals who have suffered a prior episode of exertional rhabdomyolysis may remain in a state of incomplete metabolic recovery for a considerably longer interval than is typically appreciated on the basis of creatine kinase normalization and symptomatic recovery alone, a consideration with potential, though currently unvalidated, relevance to return-to-play timing decisions discussed further in Section 16.

The G6PD deficiency, a common X-linked enzymopathy affecting an estimated 10%-14% of male African Americans, has also been proposed as a potential co-factor that might interact with SCT to precipitate rhabdomyolysis, though the genome-wide association study discussed above found no evidence of pathogenic G6PD mutations or accumulation of deleterious G6PD variants in its cohort, and gene-level association analysis found no significant association between G6PD and exertional rhabdomyolysis in that dataset [14]. Similarly, common variants previously proposed as modifiers of exertional muscle injury risk in the general population, including those in the genes encoding angiotensin-converting enzyme (ACE1), the muscle isoform of creatine kinase (CKM), and the fast-twitch fiber protein α -actinin-3 (ACTN3), were not confirmed as significant contributors in this SCT-specific cohort, consistent with findings from other association studies in non-SCT populations [14]. Collectively, these genetic and molecular investigations suggest that susceptibility to exertional rhabdomyolysis and ECAST in SCT carriers is unlikely to be explained by SCT alone, but rather reflects the combination of vigorous exertion with one or more additional, as-yet incompletely characterized genetic predisposing factors affecting solute transport, mitochondrial energy production, or related pathways.

9. The Clinical Syndrome of ECAST and Differential Diagnosis

A central and long-standing challenge in the clinical management of exertional collapse in SCT carriers has been distinguishing ECAST from the several other conditions that can produce collapse during or after strenuous physical activity, most importantly exertional heat stroke (EHS), sudden cardiac arrest (SCA), and exertional rhabdomyolysis (ER) from causes unrelated to SCT [2,7,8]. In an effort to systematize the clinical description of this presumed entity and to distinguish it from mechanistically better-characterized conditions, a 2011 consensus summit of military, athletic, and medical experts formally adopted the term "exercise collapse associated with sickle cell trait" (ECAST), explicitly acknowledging that the precise underlying mechanism remained unproven while affirming the clinical and epidemiological validity of the syndrome as a recognizable presentation [2].

The clinical features that are proposed to distinguish ECAST from its principal differential diagnoses have been summarized across several sources and are compiled in Table 2. Distinctively, ECAST is reported to present relatively early in a workout or conditioning session, often within minutes of maximal effort, in contrast to exertional heat stroke, which typically manifests later in a session as core temperature progressively rises [7,8]. Core temperature in ECAST is generally reported as normal or only mildly elevated (below 104°F/40°C), and critically, mental status is characteristically preserved—the athlete remains conscious, alert, and able to communicate—described in the literature as a "conscious collapse," in sharp contrast to the altered mental status, confusion, or coma that defines exertional heat stroke [7,8]. The muscular presentation in ECAST is also reported to differ qualitatively from that of heat-related muscle cramping: whereas heat cramps typically involve sustained, painful contraction of large working muscle groups, ECAST is described as producing more diffuse, milder muscle pain accompanied by progressive weakness, such that the athlete gradually loses the ability to support body weight and "slumps" to the ground, rather than experiencing the abrupt collapse characteristic of a cardiac arrhythmic event [5,7].

Table 2. Differentiating features of exertional collapse associated with sickle cell trait (ECAST) from principal alternative diagnoses in the collapsed athlete.

Feature	ECAST	Exertional heat stroke	Sudden cardiac arrest
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Timing relative to exertion	Often early (within minutes) [7,8]	Late in session [7,8]	Variable, can be abrupt at any point [7]
Core temperature	Usually <39°C (102°F); if >40°C, treat as EHS [7]	≥40°C (104°F) [7]	Variable [7]
Mental status	Preserved ("conscious collapse") [5,7,8]	Altered, may be intermittent/subtle [7]	Abrupt loss of consciousness [7]
Muscle findings	Flaccid weakness, diffuse pain, may have muscle cramps [5,7]	May have exercise-associated muscle cramps [7]	Flaccid or seizing [7]
Urine	May be dark/bloody	Often dehydrated, may be normal	N/A [7]
Initial management	Oxygen, IV fluids, activate EMS [7]	Aggressive on-site cooling ("cool first, transport second") [7]	CPR, early AED [7]

Beyond this clinical differentiation, the presenting symptomatology of ECAST-related exertional rhabdomyolysis has been characterized in detail in the genetic cohort described previously: severe muscle pain was the most common presenting complaint (reported in 88.9% of cases with a mean severity of 7.4 out of 10 on a numerical rating scale), followed by weakness or fatigue in 60%, with exertional collapse itself documented in 53.3% of the cohort, and dark, "Coca-Cola"-colored urine reported in only 26.7%, indicating that overt myoglobinuric discoloration of urine is far from a universal or reliable early warning sign [14]. This is a clinically important point, since reliance on visibly dark urine as a screening symptom for early rhabdomyolysis would fail to identify the majority of affected individuals in this series [14]. Laboratory findings across this and related cohorts consistently demonstrate substantial elevation of serum creatine kinase, frequently reaching tens of thousands to several hundred thousand international units per liter, together with variable degrees of acute kidney injury (13.3% in the genetic cohort) and compartment syndrome (16.7%) [14]. It should be emphasized that despite this constellation of findings, the diagnosis of ECAST versus rhabdomyolysis from other causes, versus early or evolving exertional heat stroke,

versus a primary cardiac event remains fundamentally a clinical judgment made under time pressure, often by first responders or athletic trainers rather than specialist physicians, which is itself a recognized source of diagnostic delay and potential misclassification of cause of death in retrospective epidemiological series [2,5,7].

This diagnostic ambiguity is further compounded by the fact that the various proposed differentiating features summarized in Table 2 are drawn largely from expert consensus and clinical experience rather than from prospectively validated diagnostic algorithms tested against a gold-standard reference diagnosis; no study identified in the literature reviewed here has formally evaluated the sensitivity, specificity, or interobserver reliability of these clinical features when applied by frontline responders under real-world field conditions. This represents a specific and clinically consequential gap: given that early, correct identification of the likely diagnosis materially affects initial management—cooling for suspected heat stroke, cardiopulmonary resuscitation and defibrillation for suspected cardiac arrest, oxygen and rapid transport for suspected ECAST—the absence of validated diagnostic criteria for distinguishing these entities in real time represents an area where future prospective, ideally multi-site, clinical research could meaningfully improve outcomes.

10. Exertional Rhabdomyolysis: Broader Context and Relationship to SCT

To properly situate the specific risk conferred by SCT, it is necessary to consider exertional rhabdomyolysis (ER) as a broader clinical entity that occurs across the general athletic population, with or without SCT. Rhabdomyolysis is defined as a clinical syndrome of muscle breakdown releasing intracellular contents—myoglobin, creatine kinase, potassium, and organic acids—into the systemic circulation, with the potential for downstream complications including acute kidney injury, compartment syndrome, hyperkalemic cardiac arrhythmia, and, in severe cases, disseminated intravascular coagulation [7,21]. Exertional rhabdomyolysis specifically refers to muscle breakdown precipitated by unaccustomed, excessive, prolonged, or repetitive exercise, with eccentric muscle contractions—those in which the muscle lengthens under tension, as in downhill running or the lowering phase of resistance exercises—recognized as a particularly potent mechanical trigger owing to the greater shear stress placed on the sarcolemma [21].

A comprehensive review of exertional rhabdomyolysis in amateur athletes has characterized the underlying pathophysiological cascade as beginning with critical depletion of intracellular ATP

during high-volume eccentric loading in unconditioned individuals, which impairs the function of sodium-potassium and calcium ATPase pumps, leading to pathological intracellular calcium sequestration; this in turn activates calcium-dependent proteolytic enzymes, including calpains and phospholipases, that degrade the sarcolemma and precipitate efflux of myoglobin and other intracellular contents into the circulation [21]. Once in the circulation, myoglobin is proposed to produce acute kidney injury through a "nephrotoxic triad": renal vasoconstriction mediated by myoglobin's scavenging of nitric oxide, direct tubular cytotoxicity via Fenton-reaction-generated reactive oxygen species arising from dissociated ferrous iron in the acidic tubular environment, and physical tubular obstruction by pigmented casts formed when myoglobin cross-links with Tamm-Horsfall protein under conditions of low urinary pH [21].

Notably, this broader review identifies sickle cell trait as one specific intrinsic physiological vulnerability among several recognized risk factors for exertional rhabdomyolysis, situating it alongside other contributors including inadequate hydration and hyponatremia, hypokalemia (which can precipitate arteriolar vasoconstriction and local muscle ischemia during exercise), eccentric biomechanical loading, thermal strain, and the widespread unsupervised use of nonsteroidal anti-inflammatory drugs, which inhibit prostaglandin-mediated afferent arteriolar vasodilation and thereby compound the vasoconstrictive nephrotoxic effects of circulating myoglobin [21]. This broader framing is clinically important: it situates SCT not as a unique or isolated cause of exertional rhabdomyolysis, but as one identifiable risk factor operating within a multifactorial etiological framework in which environmental, pharmacological, and training-related factors frequently interact with, and may sometimes outweigh, genetic predisposition.

This point is reinforced when comparing the clinical severity of exertional rhabdomyolysis cases attributed principally to SCT against cases occurring in the general athletic population without SCT: the case reports and cohort studies reviewed here document peak creatine kinase values in the range of tens of thousands to several hundred thousand IU/L regardless of SCT status, and acute kidney injury and compartment syndrome are documented complications in both SCT-positive and SCT-negative exertional rhabdomyolysis populations, suggesting that the downstream clinical severity and management of established rhabdomyolysis is, once the muscle injury cascade has been initiated, largely independent of the specific underlying trigger, whether that trigger be SCT, unaccustomed eccentric exercise, dehydration, or concurrent supplement use [14,21-23]. This observation has direct clinical implications: while establishing SCT status may be relevant to risk

stratification, prevention counselling, and, in some settings, longer-term return-to-play planning, it does not appear, on the basis of currently available evidence, to materially alter the acute management approach once a diagnosis of exertional rhabdomyolysis has been established.

The diagnostic challenges of exertional rhabdomyolysis are compounded by the fact that the classic textbook triad of muscle pain, weakness, and dark urine is present in fewer than 10% of confirmed cases, with over half of patients reporting no muscle pain or weakness at all in some series, and symptoms typically displaying a delayed onset of 24 to 72 hours after the precipitating exertion, closely mimicking the far more common and benign phenomenon of delayed-onset muscle soreness [21]. Serum creatine kinase remains the diagnostic gold standard, with a diagnosis typically confirmed at levels exceeding five times the upper limit of normal (generally greater than 1,000 IU/L), though levels may not peak until 24 to 72 hours after exertion, meaning a single early normal value does not exclude the diagnosis [21]. Serum myoglobin, despite being the proximate nephrotoxin, is a notoriously unreliable diagnostic marker owing to its short plasma half-life of approximately two to three hours, which can produce false-negative results if testing is delayed even by a day [21]. Serum creatinine is similarly confounded in muscular athletic populations, since creatinine is itself a muscle-derived breakdown product, such that individuals with high muscle mass may show falsely elevated baseline creatinine, while acute muscle wasting can produce misleadingly low values; cystatin C has been proposed as a muscle-mass-independent alternative marker of renal function in this context, though its use remains investigational in the sports medicine literature reviewed here [21].

11. Case Reports Illustrating the Clinical Spectrum

Individual case reports, while limited in generalizability, provide important texture to the epidemiological and mechanistic literature by illustrating the real-world clinical presentation, diagnostic uncertainty, and management of SCT-associated exertional injury. A widely cited case describes a 28-year-old previously healthy Hispanic woman who developed severe bilateral leg pain and dark urine three days after her first participation in a high-intensity indoor cycling ("spin") class, having not regularly engaged in vigorous exercise beforehand and having consumed little water before or during the 45-minute session [24,25]. She presented with a serum creatine kinase of 74,978 IU/L, was treated with aggressive intravenous isotonic saline and sodium bicarbonate, and was discharged with declining creatine kinase and normal renal function throughout her

admission; only at outpatient follow-up was hemoglobin electrophoresis performed, revealing an SCT pattern (HbA 57.8%, HbS 37.6%) that had been entirely unknown to the patient prior to this event [24,25].

This case is instructive for several reasons beyond its clinical details. First, in the revised version of this case report, the authors explicitly grappled with the difficulty of causal attribution, acknowledging that the patient's rhabdomyolysis was "likely multifactorial," potentially attributable to inadequate hydration and lack of prior conditioning independent of her SCT status, and that SCT, given its high population prevalence and the fact that the overwhelming majority of carriers never develop rhabdomyolysis, may in this instance have been an incidental finding rather than a causal contributor [25]. This candid methodological reconsideration between the original and revised versions of the same case report is itself a valuable illustration of the broader epistemological difficulty pervading this literature: because SCT is common and rhabdomyolysis, even in SCT carriers, remains uncommon, individual case reports can rarely establish causation with confidence, and the field has at times been criticized for over-attributing causal significance to SCT based on case-level coincidence alone [2,25]. Second, spin-class-associated rhabdomyolysis has itself been separately identified in the broader sports medicine literature as producing disproportionately severe biochemical derangement and longer hospital admissions compared with rhabdomyolysis from other exertional causes, a pattern the original case report authors specifically invoked as heightening the theoretical concern for individuals with unrecognized SCT undertaking their first high-intensity spin session [24].

A second illustrative case describes a 31-year-old woman with a recent history of mild coronavirus disease 2019 (COVID-19) infection three weeks prior, who developed severe rhabdomyolysis (peak creatine kinase 120,053 U/L) and stage 3 acute kidney injury (peak serum creatinine 8.5 mg/dL) after a modest bout of exercise—a 2.4-kilometer run, push-ups, and sit-ups completed in under twenty minutes—that would not typically be expected to produce such severe muscle injury in a healthy individual [22]. This patient required thirteen days of hospitalization with aggressive intravenous hydration and sodium bicarbonate but did not require dialysis, and was only found to have SCT (HbS 38.8%) on outpatient hemoglobin electrophoresis performed after discharge, once the severity and rapidity of her renal and muscular injury prompted the treating team to search for an underlying etiological substrate beyond the moderate exercise and recent viral illness [22]. The authors explicitly framed this case as illustrating a compounding interaction between prior viral

infection—potentially producing residual inflammatory or microvascular injury—and SCT-related susceptibility to exertional muscle damage, though they appropriately acknowledged that this represents a single observation rather than established mechanistic proof [22].

A third case, presenting a markedly different clinical picture, describes a 25-year-old male Service Member without known SCT status who developed severe exertional rhabdomyolysis (peak creatine kinase >100,000 U/L) with acute kidney injury (serum creatinine 3.9 mg/dL) and severe hyperkalemia (6.2 mmol/L) after a single high-intensity CrossFit-style workout undertaken with inadequate hydration and concurrent creatine supplementation, without any mention of underlying hemoglobinopathy [23]. This case, while not itself an SCT case, is relevant to the present review because it exemplifies the broader phenomenon of severe exertional rhabdomyolysis occurring in young, apparently healthy individuals during high-intensity functional training modalities that have become increasingly popular, underscoring that SCT is one risk factor among several—alongside dehydration, unaccustomed exercise, and supplement use—that can converge to produce a common final clinical pathway of explosive muscle breakdown and acute kidney injury [21,23]. This case, together with the spin-class and post-COVID cases, illustrates the recurring clinical narrative across this literature: previously healthy, often young and fit, individuals experiencing catastrophic muscle breakdown after a single bout of unaccustomed high-intensity exercise, with SCT identified as a contributing or potentially contributing factor in only a subset of cases and typically discovered only after the acute event has already occurred [22-25].

Considered together, these four cases—three involving confirmed SCT and one CrossFit-related case without SCT—collectively span a broad spectrum of exercise modalities (indoor cycling, running/calisthenics, and high-intensity functional fitness training) and precipitating circumstances (unaccustomed first exposure, recent viral illness, and creatine supplementation with dehydration), suggesting that the specific exercise modality itself may be less clinically important than the combination of unaccustomed intensity, inadequate hydration, and, in the SCT-positive cases, an underlying but previously unrecognized hemoglobinopathy. It is notable that in two of the three SCT-positive cases, the diagnosis of SCT was established only retrospectively, after the acute presentation, underscoring the broader theme—already discussed in the context of screening effectiveness—that unrecognized SCT status remains common even among patients presenting with a clinical picture in which SCT should reasonably be considered as part of the differential diagnostic workup [22,24,25].

Finally, extending this clinical picture beyond the musculoskeletal system, a case report describes acute coronary thrombosis with minimal underlying atherosclerosis in a 42-year-old male marathon runner who developed chest discomfort during a race, completed the marathon despite this discomfort, and subsequently presented with evolving anterior myocardial infarction requiring emergency coronary angiography, which demonstrated a large proximal left anterior descending artery thrombus overlying only a small rim of atherosclerotic plaque, later shown by intravascular ultrasound and virtual histology to represent a fissured plaque with superimposed thrombus rather than an occlusive atherosclerotic stenosis [26]. This patient was subsequently found to have SCT, which the authors proposed as a plausible contributing factor to the exaggerated thrombotic response following extreme physical exertion, in combination with dehydration and a heightened coagulation state, though they were careful to note that the paradoxical protective effect of the patient's excellent underlying cardiovascular fitness—which had produced unusually large coronary arteries that maintained sufficient residual flow to avoid complete infarction despite the large thrombus burden—may itself have been what allowed him to survive an event that in a less fit individual might have proven immediately fatal [26]. This case broadens the clinical spectrum of SCT-associated exertional pathology beyond skeletal muscle and kidney to encompass a plausible, if isolated, contribution to exercise-associated coronary thrombosis, and is consistent with the independently documented epidemiological association between SCT and venous thromboembolism discussed in the following section.

12. Venous Thromboembolism and Cardiovascular Considerations

Beyond the acute exertional syndrome, SCT has been independently associated with an elevated baseline risk of venous thromboembolism (VTE), a finding with direct relevance to the broader clinical risk profile of SCT carriers, including athletes. A large population-based cohort study using the UK Clinical Practice Research Datalink, encompassing 30,424 individuals screened for sickle cell status across 609 general practices with 179,503 person-years of follow-up, identified 55 VTE events among 6,758 SCT carriers and 125 VTE events among 23,666 non-carriers, corresponding to an incidence of 14.9 per 10,000 person-years in carriers versus 8.8 per 10,000 person-years in non-carriers [18]. In a nested case-control analysis adjusting for body mass index, pregnancy, smoking status, and ethnicity, SCT carriers remained at significantly increased risk of VTE (odds ratio 1.78, 95% confidence interval 1.18-2.69), with the elevation in risk driven predominantly by pulmonary embolism specifically (odds ratio 2.27, 95% confidence interval 1.17-4.39) rather than

deep venous thrombosis, for which the increase in risk did not reach statistical significance (odds ratio 1.43, 95% confidence interval 0.79-2.59) [18]. This finding is broadly consistent with earlier, smaller studies conducted predominantly in hospitalized African American populations, which similarly reported an elevated risk of pulmonary embolism specifically, without a comparably clear signal for deep venous thrombosis [18].

An expert panel opinion on the clinical management of SCT similarly concludes, based on review of the available literature, that SCT should be regarded as a modest, independent risk factor for venous thromboembolism, comparable in magnitude to other recognized weak thrombophilic risk factors, though the panel explicitly notes that current evidence is insufficient to recommend routine thrombophilia screening in all SCT carriers, and that decisions regarding anticoagulation intensity or duration should not be altered on the basis of SCT status alone in the absence of further prospective data [1]. This same expert panel document addresses a wide range of additional SCT-associated clinical considerations relevant to the broader medical management of athletes and other carriers, including an increased risk of renal medullary carcinoma (a rare but highly aggressive malignancy presenting almost exclusively in SCT carriers, typically under age 40, with hematuria as the most common and often earliest presenting sign), an increased risk of chronic kidney disease and progression to dialysis, and a documented, though incompletely characterized, association with splenic infarction at high altitude, particularly in unacclimatized individuals undertaking mountaineering or unpressurized air travel [1].

The mechanistic basis proposed for the elevated VTE risk in SCT parallels, in important respects, the mechanistic hypotheses invoked for exertional muscle and renal injury: chronic, low-grade endothelial activation and a mildly procoagulant state, potentially related to the same hemorheological abnormalities—elevated blood viscosity, altered erythrocyte membrane properties, and heightened cell adhesion—implicated in the exertional collapse literature discussed in Section 6 [1,13,18]. This convergence suggests that SCT may confer a generalized, low-grade prothrombotic and hemorheological tendency that manifests clinically along a spectrum, from asymptomatic laboratory abnormality in the majority of carriers, through modestly elevated baseline VTE risk, to, in rare and likely multifactorially determined cases, acute exertional muscle and renal injury or even coronary thrombosis under conditions of extreme physiological stress. This unifying hypothesis, while conceptually appealing, has not been directly tested in a single study designed to examine both exertional collapse risk and baseline thrombotic risk in the same

cohort, and remains, at present, an interpretive synthesis rather than an established mechanistic pathway.

Regarding cardiac considerations specifically in the context of competitive sports participation, updated professional society recommendations for athletes with cardiovascular disease include a dedicated task force addressing SCT for the first time in the 2015 revision of joint American Heart Association and American College of Cardiology eligibility and disqualification guidelines, a departure from the 2005 predecessor document, which did not separately address the condition [27]. The updated guideline explicitly frames known precipitating factors for SCT-related sudden death as including training at high ambient temperature or high altitude, particularly following a period of deconditioning, and notes the distinctive prodromal presentation of cramping, dyspnea, and progressive muscle pain and weakness that differentiates this presentation from the immediate loss of consciousness characteristic of other causes of sudden cardiac arrest [27]. Consistent with the general shift in this guideline document away from blanket restriction and toward individualized, evidence-informed risk mitigation, all recommendations specific to SCT are classified as Class I preventive measures—hydration, rest, awareness of acute management strategies, and caution in extremes of temperature or altitude—rather than restriction from competitive sports participation, reflecting the consensus view that identified SCT status represents an opportunity to implement targeted precautions while preserving continued athletic participation, rather than a basis for disqualification [27].

13. Comparative Physiology: Sickle Cell Anemia, Aerobic Capacity, and the Distinct Case of SCT

To properly contextualize the relatively modest physiological burden of SCT, it is instructive to briefly contrast it with the substantially more severe cardiopulmonary and exercise-capacity impairment documented in individuals with homozygous sickle cell anemia (SCD, HbSS). A prospective cross-sectional study comparing sixty children and young adults with sickle cell anemia (HbSS or HbS β 0-thalassemia) against thirty matched controls without SCT or SCD, using maximal graded cardiopulmonary exercise testing with breath-by-breath gas exchange analysis, found that subjects with sickle cell anemia demonstrated significantly lower peak oxygen consumption (26.9 mL/kg/min versus 37.0 mL/kg/min in controls, $p < 0.001$), lower peak work rate, slower and less efficient oxygen uptake, lower oxygen pulse (a surrogate for stroke volume), and

reduced ventilatory efficiency, findings attributable to complex derangements in cardiopulmonary and metabolic responses to exercise that persisted even after statistical adjustment for the degree of chronic anemia [28]. Critically, this study also established that maximal cardiopulmonary exercise testing itself was safe in this severely affected population, with no serious adverse events, including no precipitation of vaso-occlusive pain crisis, occurring during or within two weeks after testing in any of the sixty subjects with sickle cell anemia [28].

This comparison is instructive on two levels. First, it demonstrates unambiguously that the substantial cardiopulmonary limitation and exercise intolerance documented in true sickle cell anemia—driven by chronic anemia, pulmonary vascular disease, and cardiac dysfunction—simply does not apply to the pathophysiology of SCT, in which resting hemoglobin concentration, cardiopulmonary function, and baseline exercise capacity are essentially normal [1,28]. Second, and perhaps counterintuitively, it underscores that the risk conferred by SCT during exercise is not one of generally reduced exercise capacity or tolerance, since SCT carriers can and regularly do achieve elite levels of athletic performance, but rather a narrower, situationally triggered risk of catastrophic collapse under specific conditions of extreme, sustained, maximal exertion, particularly when compounded by heat, dehydration, and altitude [2,5,7]. This distinction has direct clinical relevance: whereas exercise prescription and cardiopulmonary risk stratification in sickle cell anemia must account for genuinely reduced baseline aerobic capacity and cardiovascular reserve, exercise management in SCT is properly conceptualized as a matter of situational risk mitigation during specific high-intensity training modalities rather than a broader restriction on physical activity or athletic participation [1,2,28].

This distinction also carries important implications for how clinicians counsel patients and families upon disclosure of a positive SCT result, a moment that can otherwise generate disproportionate anxiety if SCT is conflated, even inadvertently, with sickle cell disease in the mind of the patient or family. Given the demonstrated normal baseline cardiopulmonary function and exercise capacity in SCT, and given that the great majority of carriers, including many elite athletes, never experience any adverse exertional event, appropriately calibrated counselling should emphasize the fundamentally different natural history of SCT compared with SCD, while still conveying the genuine, if situationally specific and individually variable, need for exertional precautions under conditions of extreme heat, altitude, dehydration, or unaccustomed maximal-effort conditioning [1,2,28].

Relevant to the broader physiological context of hematological conditions in athletes, it is also worth noting that SCT carriers must be distinguished from athletes with acquired or non-genetic causes of anemia or altered hematological parameters, since the differential diagnosis of reduced hemoglobin or abnormal iron indices in athletes encompasses a substantially broader range of etiologies, including so-called "sports anemia" from exercise-induced plasma volume expansion, iron deficiency from increased demand, gastrointestinal and genitourinary blood loss, exercise-induced hemolysis from mechanical footstrike trauma, and inflammation-mediated hepcidin elevation, none of which are specific to or diagnostic of SCT [29]. Clinicians evaluating an athlete with unexplained fatigue, hematuria, or abnormal complete blood count parameters should therefore consider SCT as one element within this broader differential, to be confirmed by hemoglobin electrophoresis, rather than inferred from nonspecific hematological findings alone [1,29].

14. Screening Policy: Rationale, Implementation, and Effectiveness

The 2010 NCAA Division I mandatory SCT screening policy, subsequently extended to Divisions II (2012) and III (2014), required incoming student-athletes to establish their SCT status through one of three pathways: documentation of a prior test result, undergoing a sickle cell solubility test, or, in the policy's original and long-retained form, signing a written waiver declining testing and releasing the institution from associated liability [2,11]. This waiver option was formally eliminated across all divisions effective August 2022, such that all incoming NCAA athletes are now required to establish SCT status through testing or documented prior results, without the option to decline [11]. As detailed in Section 4, this policy has been associated with an 85%-88% reduction in the incidence of SCT-related fatalities in NCAA Division I football specifically, alongside a divergent trend of increasing SCT-related fatality rates at the high school level, where no comparable mandatory screening framework exists [9,12].

The most comprehensive empirical evaluation of the policy's implementation and stakeholder attitudes to date, a national mixed-methods survey study, collected responses from 168 sports medicine administrators (head athletic trainers and team physicians), 268 athletic staff (staff athletic trainers and coaches), and 1,424 athletes across 123 participating NCAA institutions spanning basketball, football, soccer, lacrosse, and track and field [11]. This survey found broadly high levels of support for the core screening requirement across all three respondent groups—

84.6% of sports medicine administrators, 93.2% of athletic staff, and 87.3% of athletes agreed or strongly agreed that athletes should be required to establish SCT status—but revealed considerably more heterogeneous and, in several respects, more skeptical attitudes toward specific aspects of policy design and implementation [11]. Notably, 41% of sports medicine administrators, 49.8% of athletic staff, and 51.1% of athletes agreed or strongly agreed that "screening for other conditions, such as arrhythmia, is more important" than SCT screening, suggesting a substantial minority view among all stakeholder groups that SCT screening may be disproportionately emphasized relative to other cardiovascular screening priorities [11].

Perhaps most striking, and directly relevant to the ethical controversy discussed in the following section, the survey found that support for targeted rather than universal screening—restricting screening to sports deemed to place athletes at greater risk of overexertion, or to athletes from racial or ethnic groups in which SCT is more common—had risen substantially compared with an earlier, smaller single-state survey conducted approximately three years after policy implementation [11]. In the more recent national survey, 51.3% of sports medicine administrators, 58.4% of athletic staff, and 74.7% of athletes agreed or strongly agreed that screening should focus on higher-risk sports, while 25.6%, 31.6%, and 41.8% of the respective groups agreed that screening should focus on racial or ethnic groups in which SCT is more prevalent—figures substantially higher than the single-digit-to-low-double-digit percentages reported in the earlier, smaller survey [11]. Multivariable regression analysis in this study found that higher SCT knowledge scores among athletes were independently associated with lower odds of agreeing that screening should be race/ethnicity-targeted or that precautions for SCT-positive athletes were unrealistic, suggesting that improved education may counteract, rather than reinforce, support for potentially discriminatory targeted-screening approaches [11]. Conversely, athletes identifying as Black or of other non-White race were more likely than White athletes to agree that expecting SCT-positive athletes to consistently apply exercise precautions was "not realistic," a finding the study authors interpreted as potentially reflecting lived experience of the practical difficulty of modifying behavior within team training environments, though this interpretation was necessarily speculative given the survey's cross-sectional design [11].

This apparent trend toward increasing support for targeted, rather than universal, screening over time is itself noteworthy and, arguably, concerning from a policy perspective, since it runs directly counter to the position articulated by major hematology professional societies, and it raises the

possibility that a decade of practical policy implementation may have inadvertently normalized a targeted-screening mindset among athletic stakeholders, rather than reinforcing the universal-precautions framework favored by hematology experts [2,3,11]. Whether this shift in stakeholder attitudes reflects genuine, evidence-based reasoning about comparative risk across sports and populations, or reflects a more general, less critically examined assumption that SCT is predominantly "a Black athlete's problem," cannot be determined from the survey data alone, and represents an important area for further qualitative and educational research.

Independent evaluation using a different methodology—retrospective review of preparticipation evaluation forms rather than survey attitudes—found that self-reported SCT screening substantially underestimates true SCT prevalence among high school athletes. In a review of 401 preparticipation evaluation forms from a Florida orthopedic sports medicine clinic, only six of 162 confirmed Black athletes (3.7%) self-reported a positive SCT diagnosis, compared with the 7.3% national prevalence reported by the Centers for Disease Control and Prevention for the Black/African American population, representing a self-reported rate approximately 50% below the expected value [30]. Furthermore, 21 of 162 (13%) Black athletes and 44 of 401 (11%) athletes overall left the SCT-specific question on the preparticipation form entirely blank, a substantially higher non-response rate than the comparable American Heart Association cardiac screening questions on the same form, which had a combined blank-response rate of only 4.5% [30]. This discrepancy suggests either that a meaningful proportion of athletes and their families are simply unaware of previously documented SCT status—despite universal newborn screening for hemoglobinopathies having been mandated across all fifty United States since 2006—or that some proportion of respondents may be declining to disclose known SCT status, potentially reflecting concern regarding stigmatization or discrimination, though the retrospective design of this study could not distinguish between these two possible explanations [30]. This finding has direct practical implications: it demonstrates that self-report-based screening methodologies, as employed at the high school level in the absence of NCAA-style mandatory laboratory testing, are likely to substantially undercount true SCT prevalence and therefore fail to identify a meaningful proportion of at-risk athletes for targeted precautions [30].

The disproportionately high blank-response rate on the SCT question, relative to the cardiac screening questions on the same form, is itself a finding worth dwelling upon, since it suggests that families may perceive the SCT question differently from other medical screening questions—

perhaps as less relevant, less well understood, or more sensitive to disclose—than standard cardiac history questions. This observation, taken together with the survey data discussed above regarding stakeholder attitudes toward targeted screening, suggests that effective SCT screening at any level of competition likely requires not merely the existence of a screening requirement or form field, but active clinical engagement, explicit explanation of the purpose and reassuring nature of the screening (that is, that a positive result does not preclude athletic participation), and, ideally, laboratory confirmation rather than reliance on family recall or self-report alone [11,30].

15. The Ethical and Scientific Controversy Surrounding Screening

The scientific and ethical debate surrounding mandatory SCT screening in athletics remains genuinely unresolved and deserves to be presented with the full weight of the disagreement it has generated, rather than resolved artificially in favor of either position. Proponents of screening, drawing primarily on the epidemiological data discussed in Section 4 documenting reduced fatality rates in NCAA Division I football following the 2010 policy, argue that knowledge of SCT status enables targeted, individualized precautions—modified pacing, mandatory rest intervals, closer medical supervision during high-risk conditioning drills—that meaningfully reduce catastrophic risk without imposing disproportionate burden, and that the empirical decline in fatalities associated with policy implementation, while imperfect as causal evidence, constitutes a meaningful real-world signal that should not be dismissed [2,9,10,12].

Opponents, most prominently the American Society of Hematology, the Sickle Cell Disease Association of America, and other affiliated professional and public health bodies, have articulated several distinct lines of objection [2]. First, they argue that mandatory genetic screening restricted to a condition disproportionately affecting Black athletes risks perpetuating a form of race-based medical surveillance with a documented historical association with employment and insurance discrimination, and that the psychological and social costs of such targeted testing may not be justified given the low absolute risk of adverse events even among untested SCT carriers [2,3,11]. Second, and more fundamentally, this position holds that the underlying causal mechanism attributed to SCT-related death—acute sickle cell crisis and vaso-occlusion—lacks robust scientific support, as articulated in the recent commentary reviewing the American Society of Hematology's systematic evidence review, which found no valid comparative studies establishing "sickle cell crisis" as a clinical entity in SCT and concluded that the label should not appear on

death certificates as a cause of death [3]. Third, opponents argue that universal precautions—applied to all athletes regardless of documented SCT status, encompassing graduated training intensity, adequate rest intervals, aggressive hydration protocols, and heat acclimatization—achieve comparable or superior protective benefit without the need for genetic testing at all, a position substantially supported by the historical United States Army experience, in which universal environmental and exertional precautions, implemented in the absence of mandatory SCT screening, were associated with elimination of the excess mortality previously observed in SCT-positive recruits [2,5].

This latter point deserves particular emphasis because it is directly supported by the large cohort study of 47,944 Black soldiers discussed in Section 4, which found that under conditions of universal exertional-injury precautions already in place across the entire United States Army, SCT carriers experienced a significantly elevated risk of exertional rhabdomyolysis but no significantly elevated risk of death from any cause compared with non-carriers [19]. This finding directly complicates the narrative, prevalent in much of the athletic screening literature, that SCT-specific knowledge and targeted precautions are necessary to prevent excess mortality; instead, it suggests that sufficiently robust universal precautions, applied without regard to individual SCT status, may themselves be adequate to eliminate the excess mortality risk, even while a residual, statistically significant excess risk of the non-fatal complication of exertional rhabdomyolysis persists [19]. Reconciling this Army-derived evidence with the NCAA football fatality data discussed in Section 4 is genuinely difficult: it is possible that the specific demands of American football conditioning—particularly serial maximal-effort sprinting drills and "gasser" runs historically implicated in several fatal cases—impose a qualitatively different and more concentrated physiological stress than typical military conditioning, such that universal precautions alone, without SCT-specific individualized modification, may be insufficient in that particular training context [5,9,12]. Alternatively, it is possible that the observed decline in NCAA football fatalities following 2010 reflects concurrent improvements in general conditioning oversight and reduced tolerance for the historically documented pattern of coach-directed "punishment" conditioning drills, rather than a specific causal effect of SCT knowledge per se [10,12].

This latter interpretation is directly supported by independent analysis of the same broader dataset of non-traumatic football fatalities, which found that the great majority of such deaths, across all causes including SCT, sudden cardiac arrest, and exertional heat stroke, occurred not during games

or standard in-season practices but during off-season or preseason conditioning sessions specifically, frequently characterized by what the authors termed "irrationally intense workouts and/or punishment drills" conducted under inadequate medical supervision [10,12]. A separate commentary from an experienced collegiate athletic trainer, reviewing sixteen years of NCAA football nontraumatic fatalities, argued forcefully that these deaths reflect a persistent institutional failure to apply established principles of exercise physiology to off-season conditioning design, rather than representing an inevitable or unavoidable consequence of any single underlying medical condition, including SCT [10]. This commentary specifically highlighted that the 2003 NCAA football out-of-season model, which mandated a structured acclimatization period at the start of preseason practice, did not achieve a statistically significant reduction in exertional heat stroke fatalities, in contrast to the more substantial apparent effect observed for the 2010 SCT screening bylaw, a discrepancy the author attributed to the acclimatization model's narrow focus on the first five days of preseason while leaving conditioning practices during the remainder of the year, including notoriously intense winter and summer conditioning sessions, essentially unregulated [9,10].

Taken together, these three lines of evidence—the Army mortality data, the football fatality data, and the institutional commentary on conditioning practices—suggest a working synthesis in which the specific behavioral and institutional context of American collegiate football conditioning, historically characterized by punitive or excessively intense off-season workouts with limited medical oversight, may itself represent a modifiable risk amplifier that interacts with, rather than being independent of, underlying SCT status. Under this synthesis, the apparent effectiveness of the 2010 screening bylaw might be attributable not solely, or even primarily, to the genetic information itself, but to the broader institutional and cultural shift in awareness, oversight, and accountability that accompanied its introduction—including heightened attention from athletic training staff, greater willingness to intervene in and modify punitive conditioning practices, and increased scrutiny of conditioning-related fatalities more generally. If this interpretation is correct, it would suggest that universal precautions, if implemented with the same degree of institutional seriousness, oversight, and accountability that has accompanied the SCT screening bylaw, might in principle achieve comparable protective benefit without the specific ethical costs associated with race-correlated genetic screening—though this remains, at present, an unproven hypothesis rather than an established conclusion, since no controlled comparison of "universal precautions with high

institutional oversight" versus "SCT-specific screening" has been conducted in the collegiate football setting.

16. Prevention Strategies and Return-to-Play Considerations

Regardless of one's position in the screening debate, there is substantially broader consensus across the reviewed literature regarding the specific preventive measures that should be applied to SCT carriers engaged in intense athletic or military training, and indeed many of these measures overlap substantially with general best-practice recommendations for the prevention of exertional heat illness and rhabdomyolysis in all athletes regardless of SCT status [1,2,7]. Recommended precautions for known SCT carriers include a gradual, individualized approach to conditioning intensity that allows the athlete to set their own pace rather than being forced to match group performance standards, exclusion from serial maximal-effort sprint testing or timed-mile assessments that concentrate extreme exertional demand into a short interval, provision of adequate rest intervals between repetitions rather than continuous maximal effort, mandatory and closely monitored hydration before, during, and after training, adjustment of training intensity and duration in conditions of high ambient heat or high altitude, and immediate cessation of activity with prompt medical evaluation at the first sign of unusual muscle weakness, cramping, or breathing difficulty [1,2,7].

An expert panel opinion addressing the broader medical management of SCT carriers similarly concludes that individuals with SCT should not be restricted from athletic participation, including at a competitive level, but that appropriate individualized precautions, awareness on the part of coaches and training staff, and prompt symptom-triggered cessation of activity are essential components of safe participation [1]. This same panel addresses several situational contexts relevant to athletes with SCT, including altitude exposure, where splenic infarction has been documented predominantly in male SCT carriers undergoing rapid ascent to high altitude (generally above the 2,000-2,500 meter range typical of most training or competition venues), with the panel recommending a structured, gradual acclimatization program for SCT carriers undertaking mountaineering or high-altitude training, while noting that SCT carriers native to or long-resident at high altitude do not appear to experience the same risk, consistent with a protective effect of physiological acclimatization [1].

Regarding acute management of a suspected ECAST event, the reviewed literature is consistent in recommending immediate cessation of the inciting activity, assessment of airway, breathing, and circulation, measurement of core temperature to exclude concurrent or evolving exertional heat stroke (with aggressive on-site cooling initiated immediately if temperature exceeds 40°C/104°F, following the "cool first, transport second" principle established for heat stroke management), provision of supplemental oxygen, establishment of intravenous access for aggressive fluid resuscitation, and prompt transport to an emergency facility with explicit communication to receiving staff regarding the possibility of fulminant rhabdomyolysis, given the potential for extremely rapid clinical deterioration [5,7,8,21]. Once the diagnosis of exertional rhabdomyolysis is established or strongly suspected, management follows the standard approach for this condition regardless of underlying SCT status: aggressive intravenous isotonic fluid resuscitation targeting a urine output of 200-300 mL/hour (or approximately 3 mL/kg/hour) to promote renal clearance of myoglobin, continuous cardiac monitoring given the risk of hyperkalemia-associated arrhythmia, and close serial monitoring of renal function, electrolytes, and creatine kinase trends, with renal replacement therapy reserved for cases complicated by refractory hyperkalemia, severe metabolic acidosis, or volume overload [21-23]. The historically proposed adjunctive measure of urinary alkalinization with sodium bicarbonate, intended to reduce myoglobin cast formation in the renal tubules, has weaker evidentiary support and has not been shown in comparative studies to reduce rates of renal failure beyond aggressive isotonic fluid resuscitation alone, though it continues to be used in many of the cases reviewed here, reflecting ongoing divergence between theoretical rationale and demonstrated clinical benefit [21-23].

Guidance addressing return-to-play decisions following an episode of exercise collapse associated with sickle cell trait acknowledges that no formally validated, evidence-based return-to-play protocol currently exists specific to ECAST, in contrast to the more developed risk-stratification and phased return-to-play frameworks that have been articulated for exertional heat stroke and for exertional rhabdomyolysis more broadly [7,8]. Proposed frameworks for the broader category of exertional rhabdomyolysis stratify affected athletes into "low-risk" and "high-risk" categories based on features including the rapidity of clinical recovery, presence or absence of acute kidney injury, personal or family history of myopathy or malignant hyperthermia susceptibility, and magnitude of peak creatine kinase elevation, with low-risk athletes proceeding through a structured, symptom-guided, multi-phase return to full training over several weeks, while high-risk

athletes are referred for specialist metabolic or genetic evaluation, including consideration of exercise-intolerance mutation panels or, in select cases, muscle biopsy, before any return-to-play decision is made [7,8]. Given the genetic findings discussed in Section 8 regarding both SLC44A3 variants and pathogenic mitochondrial DNA maintenance gene mutations identified in individuals with recurrent or severe ECAST, it is plausible that future refinement of these risk-stratification frameworks may specifically incorporate consideration of prior recurrent episodes, family history, and, where accessible, targeted genetic evaluation for SCT carriers with a documented history of ECAST or exertional rhabdomyolysis, though such genetically informed return-to-play protocols remain investigational rather than established clinical practice at present [8,14,16].

A further consideration relevant to return-to-play decision-making, though not currently incorporated into any published protocol identified in the reviewed literature, concerns the persistence of the muscle transcriptomic abnormalities documented at six months post-episode in the RNA sequencing study discussed in Section 8, which found ongoing suppression of mitochondrial oxidative phosphorylation gene expression well beyond the typical timeframe of clinical and biochemical recovery [20]. If skeletal muscle bioenergetic capacity remains measurably impaired for a substantially longer period than creatine kinase normalization would suggest, this raises the theoretical possibility—currently untested in any prospective study—that athletes returning to full-intensity training on the basis of normalized laboratory values alone might still harbor residual mitochondrial vulnerability predisposing to recurrent injury upon renewed exposure to maximal exertional stress. This remains speculative, and no study has yet examined whether extending the return-to-play timeline beyond current practice, or incorporating some form of functional mitochondrial assessment prior to clearance, would reduce the documented 39% recurrence rate observed in the genetic cohort discussed in Section 8, but it represents a biologically plausible and clinically actionable hypothesis for future prospective research [14,20].

17. Discussion

Synthesizing across the epidemiological, mechanistic, and policy literature reviewed in this article, several key patterns and tensions emerge that merit explicit discussion. First, the epidemiological signal linking SCT to exertional rhabdomyolysis is considerably more consistent across studies than the signal linking SCT to overall mortality. The large United States Army cohort study of nearly 48,000 soldiers found a significantly elevated hazard ratio for exertional rhabdomyolysis

but no significantly elevated risk of death from any cause under conditions of universal exertional-injury precautions, whereas the NCAA football-specific epidemiological literature, spanning multiple independent analyses of overlapping registry data, consistently documents a substantially elevated relative risk of fatal exertional collapse specifically attributed to SCT [2,5,9,12,19]. This apparent divergence likely reflects genuine differences between the two settings—American football conditioning, historically characterized by serial maximal-effort sprint drills and, in some documented cases, punitive or excessively intense workout regimens with inadequate medical oversight, may represent a qualitatively more concentrated and less well-supervised exertional stress than typical military basic training under modern, closely monitored heat-and-hydration protocols—rather than a fundamental contradiction in the underlying biology of SCT itself [2,9,10,12].

Second, the mechanistic literature reveals a field considerably more uncertain about causal pathways than the confident, sickling-centered narrative that dominates much of the popular and even some of the clinical literature would suggest. The recent, forceful hematological commentary arguing that "sickle cell crisis" lacks scientific validity as a cause of death in SCT, combined with the demonstrated unreliability of postmortem sickling as evidence of antemortem pathophysiological causation, represents a genuinely significant challenge to decades of accumulated clinical and forensic practice in this area [3,5]. At the same time, the emerging genetic literature identifying candidate modifier genes—SLC44A3 variants affecting solute transport, and pathogenic POLG and RRM2B mutations affecting mitochondrial DNA maintenance and consequently skeletal muscle energy production—offers a mechanistically plausible alternative or additive explanation for why only a small subset of the very large population of SCT carriers ever experiences catastrophic exertional collapse, while the overwhelming majority tolerate even extreme exertion without incident [14,16]. These findings suggest a more nuanced model in which SCT alone is necessary but insufficient to produce ECAST, and in which additional genetic or physiological susceptibility factors, still incompletely characterized, determine which individual carriers are truly at elevated risk under conditions of extreme exertion.

Third, the paradoxical finding of lower, not higher, blood and muscle lactate accumulation in SCT carriers during high-intensity exercise, together with the demonstrably normal to slightly compensatory hydration physiology observed in longitudinally studied Division I football players with SCT, cautions strongly against a simplistic, uniformly pathological framing of SCT exercise

physiology [13,15]. These findings raise the genuinely interesting possibility that certain physiological adaptations associated with SCT may, under most circumstances, be protective rather than harmful, potentially helping to explain both the general safety of exercise in the vast majority of SCT carriers and the disproportionate representation of SCT carriers among elite sprint athletes, a phenomenon that would be difficult to reconcile with a model in which SCT uniformly impairs exercise tolerance or safety [15].

Fourth, the screening policy debate cannot be resolved by appeal to the epidemiological or mechanistic evidence alone, because it turns substantially on value judgments regarding the acceptable trade-off between a demonstrated (if imperfectly quantified) reduction in catastrophic events and the risks of stigmatization, discrimination, and disproportionate targeting of a specific racial and ethnic subgroup for genetic screening [2,3,11]. The national survey data demonstrating substantial stakeholder support, even among athletes themselves, for race/ethnicity-targeted rather than universal screening is itself a finding requiring careful interpretation: it may reflect pragmatic recognition of the differential population prevalence of SCT, or it may reflect an underappreciation of the historical and ongoing risks of race-based genetic testing policies, and the survey's own finding that higher SCT knowledge was associated with reduced support for such targeting suggests that inadequate education, rather than deliberate discriminatory intent, may underlie much of this sentiment [11]. Finally, the persistent gap between NCAA-mandated screening at the collegiate level and largely ineffective self-report-based screening at the high school level represents an area of genuine, actionable improvement opportunity that does not require resolution of the deeper scientific and ethical controversies: regardless of one's position on whether screening should occur, the demonstrated unreliability of self-report methodology means that any screening policy relying on self-disclosure alone will systematically fail to identify a substantial proportion of the population it is intended to protect [30].

A further point of synthesis concerns the striking asymmetry, noted throughout this review, between the volume of literature addressing American football and United States military basic training on one hand, and the near-total absence of comparable data for other sports and settings on the other. Sports such as distance running, cycling, wrestling, and combat sports, all of which involve periods of extreme exertion under conditions of heat stress, dehydration, or rapid weight-cutting that would seem, on first principles, to plausibly carry analogous risk, are represented in the reviewed literature almost exclusively through isolated case reports—the spin-class case, the

post-COVID running case, the marathon coronary thrombosis case—rather than through any systematic epidemiological surveillance comparable to that available for football [22-26]. This absence of systematic data outside American football does not necessarily indicate an absence of risk in these other settings; rather, it more plausibly reflects the historical concentration of research attention and institutional screening infrastructure specifically within American collegiate and military settings, and represents a significant and largely unaddressed gap in the current evidence base.

18. Limitations of the Evidence Base

Several important limitations qualify the conclusions that can be drawn from the literature synthesized in this review. First, the epidemiological data underlying much of the field's understanding of SCT-associated exertional mortality derive from retrospective registry and case-series methodologies applied to a rare outcome; even the largest available datasets, spanning two decades of national American football fatality surveillance, capture only low tens of SCT-related deaths in total, producing wide confidence intervals around key risk estimates and rendering the field vulnerable to substantial imprecision, potential misclassification of cause of death, and limited statistical power to detect or exclude true effects of screening interventions [2,9,12]. Second, the genetic and mechanistic studies reviewed here, while methodologically sophisticated, are drawn from very small sample sizes—cohorts of two-case mitochondrial dysfunction comparisons, genome-wide association analyses in fewer than thirty confirmed cases, and lactate physiology studies in fifteen SCT carriers per arm—that are appropriately hypothesis-generating but cannot establish population-level causal effect sizes or be considered definitive without independent replication in larger, prospectively assembled cohorts [14-16]. Third, much of the case-report literature discussed in Sections 10-11, while clinically illustrative, is inherently susceptible to the limitations of single-patient observational reporting: causal attribution to SCT in these cases, as the authors of several of the reviewed reports themselves acknowledge, cannot be firmly established given the high background population prevalence of SCT and the low absolute incidence of rhabdomyolysis even among carriers, meaning that co-occurrence in an individual case does not establish that SCT was causally responsible for the observed clinical event [22,24,25].

Fourth, the postmortem determination of cause of death in fatal exertional collapse cases—the primary evidentiary basis for the historical epidemiological literature linking SCT to sudden death—is now recognized to be subject to a fundamental methodological confound, since intravascular sickling is an expected postmortem artifact in essentially all SCT carriers regardless of antemortem cause of death, raising the possibility that some historical death certifications attributing mortality to "sickle cell crisis" may have reflected diagnostic artifact rather than true underlying pathophysiology [3,5]. This limitation cannot be retrospectively corrected and introduces an unquantifiable degree of uncertainty into the historical case-series literature that forms much of the foundational evidence base for this field. Fifth, most of the epidemiological, genetic, and physiological studies reviewed here were conducted predominantly or exclusively in Black male populations, reflecting both the higher population prevalence of SCT in this demographic and the specific historical focus of military and American football research; this concentration limits the generalizability of findings to female athletes, to non-Black SCT carriers, and to athletic disciplines and training modalities outside American football and military conditioning that have received comparatively little dedicated study [2,5,13,14].

Sixth, this review is itself narrative rather than systematic in design, meaning that source selection, thematic grouping, and relative emphasis reflect the authors' judgment regarding clinical relevance rather than a prespecified, reproducible search and inclusion methodology, and the review is consequently subject to the selection and emphasis biases inherent to this format; readers should regard the synthesis presented here as a clinically oriented overview of a genuinely contested and incompletely resolved field, rather than a definitive or exhaustive systematic account. Seventh, an additional and specific limitation concerns the temporal heterogeneity of the reviewed literature, which spans several decades of clinical, epidemiological, and molecular research conducted under substantially different diagnostic, laboratory, and institutional contexts; the diagnostic criteria for exertional rhabdomyolysis, the availability and precision of hemoglobin electrophoresis and molecular genetic testing, and the general level of awareness of SCT among clinicians and athletic training staff have all evolved considerably over the period covered by the studies reviewed here, complicating direct comparison of findings across the earliest military case series from the 1960s-1980s and the most recent genetic and transcriptomic studies published within the last several years. Finally, it should be acknowledged that virtually none of the studies reviewed here were designed with sufficient statistical power specifically to test the comparative effectiveness of

universal precautions versus SCT-specific screening, meaning that the central policy question motivating much of the current controversy remains, strictly speaking, empirically untested by any single adequately powered study, and current positions on both sides of the debate necessarily rely on indirect inference from heterogeneous, non-comparable datasets.

19. Conclusions

Sickle cell trait remains, for the overwhelming majority of carriers, a benign hematological condition compatible with normal exercise tolerance, competitive athletic participation, and normal life expectancy. Nonetheless, a substantial and long-standing body of epidemiological, clinical, and mechanistic evidence links SCT to an increased relative risk of exertional rhabdomyolysis, and, in specific high-intensity training contexts, particularly American collegiate football conditioning, to an increased relative risk of catastrophic exercise-related collapse and death, even as absolute event rates remain low. The underlying pathophysiological mechanism remains genuinely contested: the historically dominant hypothesis of erythrocyte sickling precipitating microvascular occlusion under conditions of exertional hypoxia and acidosis is challenged by the well-documented unreliability of postmortem sickling as evidence of causation, while emerging genetic evidence implicating solute-transporter variants and mitochondrial DNA maintenance gene mutations offers a plausible, though still preliminary, alternative or complementary explanation for individual susceptibility among the vast majority of carriers who never experience clinically significant exertional injury. Physiological studies further complicate any simplistic pathological framing, with SCT carriers demonstrating, in some contexts, apparently protective rather than harmful adaptations in lactate metabolism and hydration physiology.

The NCAA's mandatory SCT screening policy, implemented in 2010 and subsequently strengthened by elimination of the testing waiver option in 2022, has been associated with a substantial reduction in SCT-attributed fatalities in collegiate football, though this policy remains genuinely and legitimately contested by major hematology professional societies on both evidentiary and ethical grounds, and self-report-based screening at the high school level has been shown to substantially underestimate true SCT prevalence, leaving a meaningful gap in protection for younger athletes. Given the current state of evidence, a reasonable clinical and policy position favors individualized risk stratification, targeted athlete and staff education regarding the distinctive early clinical features of exercise collapse, robust universal precautions regarding

hydration, pacing, and heat and altitude acclimatization applied to all athletes regardless of documented SCT status, and cautious, ethically considered approaches to genetic screening that avoid disproportionate targeting while still enabling informed, individualized precaution for those athletes who are aware of their carrier status.

Future research priorities should include larger, prospectively designed genetic studies to validate and extend the preliminary findings regarding SLC44A3 and mitochondrial DNA maintenance gene variants; further physiological characterization of the apparently protective metabolic adaptations documented in SCT carriers, ideally under exercise protocols more closely modeling the serial maximal-effort conditioning implicated in fatal collapse; rigorous, ideally prospective, evaluation of the comparative effectiveness of universal precautions versus SCT-specific screening and individualized modification across a broader range of athletic disciplines and training contexts beyond American football and military basic training; prospective validation of the clinical features currently used to distinguish ECAST from exertional heat stroke and sudden cardiac arrest under real-world field conditions; and dedicated investigation of SCT-associated exertional risk in populations that remain substantially underrepresented in the current literature, including female athletes, non-Black SCT carriers, and participants in endurance, combat, and weight-category sports outside the American football and military settings that have dominated research attention to date. Only through such expanded and methodologically rigorous investigation is the field likely to move beyond its current reliance on retrospective registry data, small hypothesis-generating genetic cohorts, and individual case reports, toward a more definitive, evidence-based framework for the prevention and management of exertional collapse in sickle cell trait carriers.

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