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Review

Direct in vivo strain measurements in human bone—A systematic literature review

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ABSTRACT

Bone strain is the governing stimuli for the remodeling process necessary in the maintenance of bone's structure and mechanical strength. Strain gages are the gold standard and workhorses of human bone experimental strain analysis in vivo. The objective of this systematic literature review is to provide an overview for direct in vivo human bone strain measurement studies and place the strain results within context of current theories of bone remodeling (i.e. mechanostat theory). We employed a standardized search strategy without imposing any time restriction to find English language studies indexed in PubMed and Web of Science databases that measured human bone strain in vivo. Twenty-four studies met our final inclusion criteria. Seven human bones were subjected to strain measurements in vivo including medial tibia, second metatarsal, calcaneus, proximal femur, distal radius, lamina of vertebra and dental alveolar. Peak strain magnitude recorded was 9096 $\mu\varepsilon$ on the medial tibia during basketball rebounding and the peak strain rate magnitude was $-85{,}500$ $\mu\varepsilon$/s recorded at the distal radius during forward fall from standing, landing on extended hands. The tibia was the most exposed site for in vivo strain measurements due to accessibility and being a common pathologic site of stress fracture in the lower extremity. This systematic review revealed that most of the strains measured in vivo in different bones were generally within the physiological loading zone defined by the mechanostat theory, which implies stimulation of functional adaptation necessary to maintain bone mechanical integrity.

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1. Introduction

Bone is a dynamic tissue capable of adapting to mechanical stimuli by (re)modeling structure (Turner, 1998). Bone strain plays a major role in the process of bone (re)modeling control and bone adaptation to mechanical loadings (Frost, 1987). The knowledge of bone strains during movement is key to furthering our understanding of bone adaptation mechanism and associated clinical applications, such as designing prosthesis (Martelli et al., 2008) and rehabilitation therapies (Taddei et al., 2003). Bone strain measurement in human is considered a challenging task. Human bone strains can be investigated either using experimental or mathematical methods. The experimental methods include in vivo and in vitro measurements. The in vitro strain measurements have been performed using mechanical testing machine with static loads (Finlay et al., 1982) or dynamic simulator with complex loading conditions mimicking the complexity of in vivo loading (Peterman et al., 2001). As for the mathematical modeling methods they include analytical methods (Gross and Bunch, 1989) and computational methods, such as the finite element method (Duda et al., 1998) and recently developed approach based on flexible multibody dynamics (Al Nazer et al., 2008a,b, 2011). Although the mechanical strains in bones cannot be measured in vivo without the use of an invasive procedure, it is the only procedure to record the strains as a result of normal loading. The mathematical models and the other in vitro experimental procedures represent a simulation of the in vivo condition and require the introduction of the effects of muscle, ligament and joint forces in an attempt to reproduce a realistic stress distribution. The simplifying assumptions involved in these methods increase the uncertainty of the resulting strain estimations.

Frost (1987) proposed the mechanostat theory, which illustrates the mechanical stimulus of bone to strain magnitudes resulting from different loading environments into four distinct zones. In the first zone, trivial loading zone, which is characterized by strain magnitudes smaller than 200 $\mu\varepsilon$ virtually no mechanical stimulus to bone occurs. In the second zone, physiological loading zone (200–2000 $\mu\varepsilon$), bone remodeling is maintained at a steady state, which preserves bone strength. Bone modeling is stimulated in the third zone, overload zone (2000–3000 $\mu\varepsilon$), and therefore new bone is added. Bone suffers microdamage and woven bone is added in last zone, pathological overload zone, when strain magnitude in response to mechanical loading exceeds 4000 $\mu\varepsilon$. At this zone bone is subjected to higher risk of fracture. The theory is demonstrated in Fig. 1, which has been reprinted with permission from the study of Forwood and Turner (1995).

In order to quantify the incident strains within the skeleton, in vivo implementation of strain gages on the surfaces of bone was used. The aim of the current review is to provide a comprehensive overview of literature regarding direct in vivo bone strain measurements in humans. To our knowledge, this study is the first systematic literature review devoted to direct in vivo strain measurements in human bone. A recent non-systematic review by Yang et al. (2011) discussed in vivo bone strain measurements in humans focusing primarily on the tibia. Their study took into account only three measurement locations: medial tibia, second metatarsal and distal radius and did not include the other four locations where in vivo strain measurements have taken place. The current review examines all in vivo studies conducted on human bones and discusses the clinical implications of the strain at each location of measurement within the context of the mechanostat theory.

2. Methods

2.1. Search strategy

In this systematic literature review, we used the Preferred Reporting Items for Systematic reviews and Meta-Analyses, PRISMA Checklist (Moher et al., 2009). We performed a systematic search to identify relevant articles published only in English on two databases: PubMed and Web of Science. The details of our search strategy in both databases are presented in Supplementary Appendix. We used the following keywords search in the two databases: "bone" AND "strain" AND "in vivo". No time period restriction was imposed in the search settings. Our search included all research document types including journal articles, conference papers, patents, abstracts, posters and any relevant document found on internet, such as technical reports. We reviewed the reference section and narrative reviews of the eligible studies retrieved from each database to search for any additional relevant articles that could have been overlooked by the electronic search. In addition, we checked the website, if possible, for each author of the eligible studies to search for any additional relevant studies that could be included. We did not perform a methodological quality appraisal in this systematic review because it does not suit the nature of the experimental studies we reviewed. This is due to the fact that methodological quality appraisal is appropriate for randomized and non-randomized studies seeking to investigate variables or factors affecting the outcome, such as testing the effectiveness therapy of a drug on a group of patients.

2.2. Study selection

Two authors (R.A and C.K) investigated the retrieved articles from the electronic search and selected the primary eligible articles. The primary articles were then reviewed by the other co-authors to verify the pertinence of their inclusion. We identified the duplicated manuscripts, which were published in conference proceedings and any discrepancies were discussed and a consensus opinion was reached.

3. Results

Based on our described electronic search, we retrieved 1323 studies from PubMed database and 1454 studies from Web of Science database. After exclusion of duplicate, irrelevant studies and manuscripts written in language other than English we identified 23 eligible studies. We reviewed the bibliographies

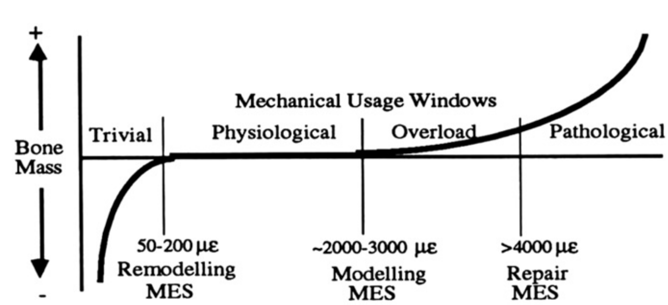

Fig. 1. Mechanostat theory relating strain magnitudes to bone response. Reprinted from Forwood and Turner (1995) copyright 1995, with permission from Elsevier Science.

from the 23 eligible studies and identified nine additional studies, which met the inclusion criteria. Of these nine studies, one original article was added bringing the total to 24 publications (Fig. 2).

Strains on different human bones have been measured in vivo and the 24 studies were sorted into seven groups (Table 1) based on strain measurement location: (1) medial tibia, (2) second metatarsal, (3) calcaneus, (4) proximal femur, (5) distal radius, (6) lamina of vertebra and (7) dental alveolar and tooth root.

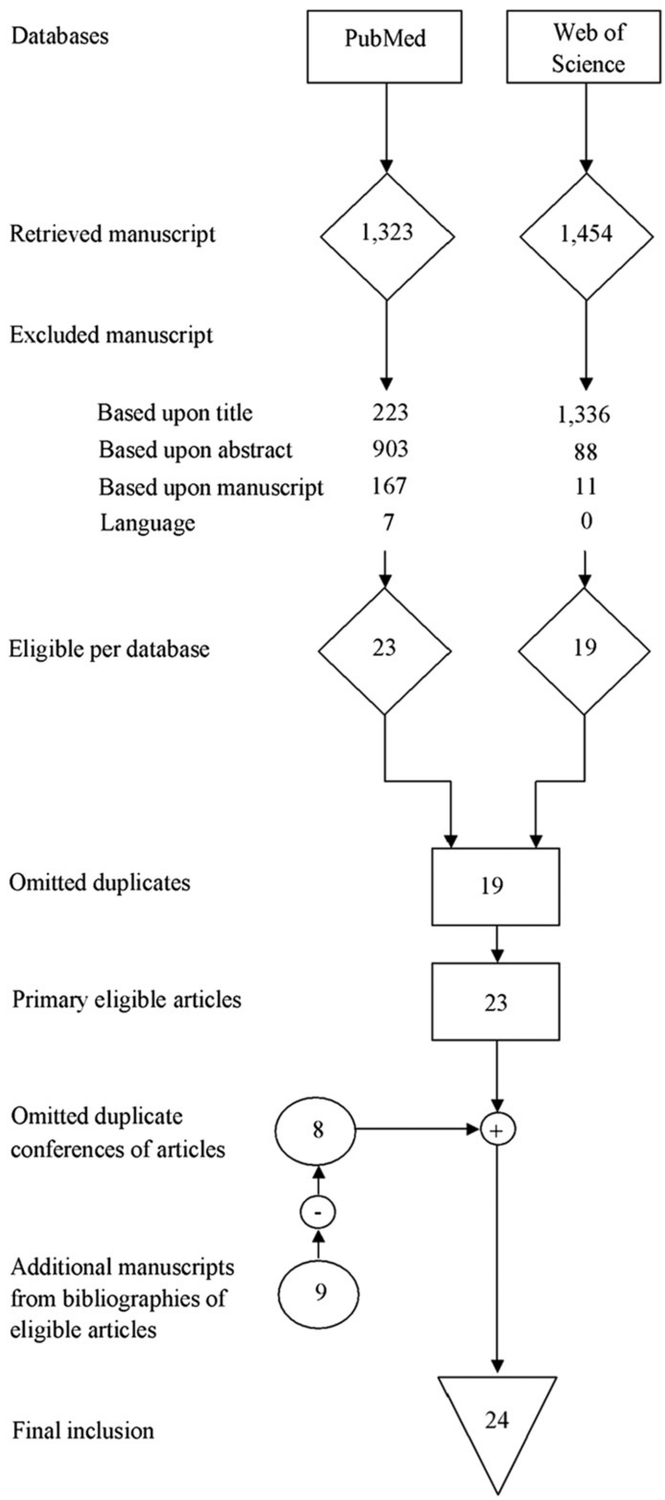

Fig. 2. Flow diagram of literature selection process.

Different types of strains and strain rates including axial, principal and peak to peak strains were reported during different activities.

4. Discussion

Due to the complex arrangement of muscles, tendons and ligaments combined with the diversity of applied loads during different normal activities, in vivo strain measurement is the only current method, which provides realistic estimation of bone strains. Strain on the human bone has been measured in vivo using three techniques: surface strain gage, staple strain gage and transcutaneous extensometer. However, these techniques are still highly invasive requiring surgical operation, limited to a number of superficial bones and highly challenging to be applied to a large population.

It is not possible to directly measure the principal bone strains: principal tensile, compression and shear strains. This is due to the fact that the principal axes are not generally known and may change with different types of activity (Burr and Milgrom, 2001). Measuring the principal bone strains at a single point requires using three strain gages placed together in a rosette pattern with each gage oriented in a different direction. Extensometer with two pins is analogous to two strain gages while extensometer with three pins is analogous to three strain gages. Therefore, it can be noticed from Table 1 that only the studies, which used three strain gages or extensometer with three pins were able to report principal strains. However, Milgrom et al. (2007) used three staple strain gages and only reported the axial strains. They explained that they were able to use only the output from two staple strain gages in their experiment.

4.1. *Locations of measurements*

4.1.1. *Medial tibia*

Stress fractures are usually caused by overtraining or overuse. Medial aspect of the tibial shaft site is clinically known to be predominant location for stress fracture in infantry recruits and athletes (Milgrom et al., 1996). For this reason and due to its being the easiest location to access compared to other bones, most of the in vivo strain measurement studies were conducted on the tibia. Several factors affecting in vivo tibial strains have been investigated including different exercises, muscle fatigue, footwear, surface types and using a cane.

Tibial strains produced by different activities ranged from daily standard activities, such as walking and running, to physical activities mimicking those done by military infantry recruits, such as zigzag running were measured in vivo. Mainly these measurements aimed to identify exercise activities, which best stimulate an increase in bone strength and thus reduce tibial stress fracture. Most of the tibial strain values measured during walking in its different states, whether it was with or without shoes, with or without load and downhill or uphill, were within a range of 237–1250 $\mu\varepsilon$, which falls in the physiological loading zone defined by the mechanostat theory. Therefore, walking can be considered as an exercise, which maintains remodeling at a steady state and thus maintains bone strength. Among all the studies that investigated walking, Lanyon et al. (1975) group was the only group who characterized tibial strain profiles produced during walking based on the phases of a walking cycle. With respect to running, the reported compressive and tensile strains in all the studies were in range of 417–2456 $\mu\varepsilon$, which is maintained well below the pathological overload zone defined by the mechanostat theory. However this is unlikely in the case for shear strains where Milgrom et al. (2000a,b,c) reported shear strains values measured during running between 5027 and 5533 $\mu\varepsilon$, which fall in the

Table 1
Overview of human bone strain measurements in vivo studies sorted out based on bone under investigation and year of publication at each location of measurement.[a]

Study	Location of measurement	Exercise	Strain (μstrain)[b]	Strain rate (μstrain/s)[b]	Techniques	Sample size (gender)[c]	Age (years)
Lanyon et al. (1975)	Antero-medial tibial mid-shaft cortex	Walk, run	$\varepsilon_{1min}=237$ (walk$_{S}$) $\varepsilon_{1max}=847$ (run$_{TB}$) $\varepsilon_{2min}=-308$ (walk$_{S}$) $\varepsilon_{2max}=-578$ (run$_{TB}$)	$\dot{\varepsilon}_{1min}=4200$ (walk$_{S}$) $\dot{\varepsilon}_{1max}=13{,}000$ (run$_{TS}$) $\dot{\varepsilon}_{2min}=-2150$ (walk$_{SL27}$) $\dot{\varepsilon}_{2max}=-4000$ (walk$_{TB}$)	45° three rosette surface strain gage	1 (M)	35
Burr et al. (1996)	Antero-medial tibial mid-shaft cortex	Walk, uphill/ downhill walk, jog, sprint, uphill/downhill run, uphill/downhill zigzag run	$\varepsilon_{1min}=381$ (walk$_{SL17}$) $\varepsilon_{1max}=743$ (run$_{SUZ}$) $\varepsilon_{2min}=-414$ (walk$_{SD}$) $\varepsilon_{2max}=-1226$ (run$_{SUZ}$) $\gamma_{min}=719$ (walk$_{SD}$) $\gamma_{max}=1966$ (run$_{SUZ}$)	$\dot{\varepsilon}_{1min}=7113$ (walk$_{SU}$) $\dot{\varepsilon}_{1max}=20237$ (sprint) $\dot{\varepsilon}_{2min}=-6437$ (walk$_{SL17}$) $\dot{\varepsilon}_{2max}=-34{,}457$ (sprint) $\dot{\gamma}_{min}=13{,}546$ (walk$_{SU}$) $\dot{\gamma}_{max}=51{,}433$ (sprint)	45° three rosette surface strain gages	2 (M)	42, 49
Milgrom et al. (1996)	Medial tibial mid-shaft cortex	Walk, run	*At walk* $\varepsilon_{1min}=543$ (walk$_{TRWS}$) $\varepsilon_{1max}=679$ (walk$_{TZB}$) $\varepsilon_{2min}=-391$ (walk$_{TZB}$) $\varepsilon_{2max}=-518$ (walk$_{TRWS}$) $\gamma_{min}=757$ (walk$_{TRS}$) $\gamma_{max}=926$ (walk$_{TRWS}$) *At run* $\varepsilon_{1min}=532$ (run$_{ZB}$) $\varepsilon_{1max}=625$ (run$_{LB}$) $\varepsilon_{2min}=-759$ (run$_{ZB}$) $\varepsilon_{2max}=-935$ (run$_{RS}$) $\gamma_{min}=1275$ (run$_{ZB}$) $\gamma_{max}=1513$ (run$_{RS}$)	*At walk* $\dot{\varepsilon}_{2min}=-2220$ (walk$_{TZB}$) $\dot{\varepsilon}_{2max}=-4436$ (walk$_{TTB}$) *At run* $\dot{\varepsilon}_{2min}=-10{,}208$ (run$_{ZB}$) $\dot{\varepsilon}_{2max}=-13{,}850$ (run$_{LB}$)	45° three rosette surface strain gage	1 (M)	49
Rolf et al. (1997)	Antero and postero medial tibial mid and distal shaft cortex, respectively.	Forward jump with forefoot landing and forward jump with heel landing	–	–	90° two staple strain gage	7 (5M, 2F)	23–33[d]
Ekenman et al. (1998)	Antero and postero medial tibial mid- and distal shaft cortex, respectively	Single jump, walk, repetitive jumps, run, drop from 45 cm	*At Antero mid* $\varepsilon_{xmin}=334$ (walk$_{S}$) $\varepsilon_{xmax}=2128$ (drop$_{S}$) $\varepsilon_{ymin}=-14$ (walk$_{S}$) $\varepsilon_{ymax}=-75$ (jump$_{Srep}$) *At Postero distal* $\varepsilon_{xmin}=436$ (drop$_{S}$) $\varepsilon_{xmax}=1796$ (jump$_{Ssin}$) $\varepsilon_{ymin}=-547$ (run$_{S}$) $\varepsilon_{ymax}=-1319$ (jump$_{Ssin}$)	–	90° two staple strain gages	1 (F)	37
Fyhrie et al. (1998)	Antero-medial tibial mid-shaft cortex	Walk before and after fatiguing exercise protocol	–	–	Transcutaneous extensometer with two pins	7 (M)	23–50[d]
Mendelson et al. (1998)	Medial tibial mid-shaft cortex	Walk with and without a cane	$\Delta\varepsilon_{ave}=169.59$ (walk$_{S}$) $\Delta\varepsilon_{ave}=169.07$ (walk$_{SCI}$) $\Delta\varepsilon_{ave}=148.29$ (walk$_{SCC}$)	$\dot{\varepsilon}_{yave}=1048$ (walk$_{S}$) $\dot{\varepsilon}_{yave}=-794.1$ (walk$_{SCI}$) $\dot{\varepsilon}_{yave}=-756.6$ (walk$_{SCC}$)	Transcutaneous extensometer with two pins	7 (M)	23–50[d]

Milgrom et al. (1998)	Medial tibial mid-shaft cortex	Walk, run	*At walk* $(\Delta\varepsilon/\Delta\varepsilon)_{min}=0.618$ (walk$_{TZ/B}$) $(\Delta\varepsilon/\Delta\varepsilon)_{max}=1.494$ (walk$_{TB/N}$) *At run* $(\Delta\varepsilon/\Delta\varepsilon)_{min}=1.077$ (run$_{Z/N}$) $(\Delta\varepsilon/\Delta\varepsilon)_{max}=1.179$ (run$_{B/N}$)	*At walk* $(\Delta\dot{\varepsilon}/\Delta\dot{\varepsilon})_{min}=0.728$ (walk$_{TZ/B}$) $(\Delta\dot{\varepsilon}/\Delta\dot{\varepsilon})_{max}=1.455$ (walk$_{TB/N}$) *At run* $(\Delta\dot{\varepsilon}/\Delta\dot{\varepsilon})_{min}=0.88$ (run$_{Z/B}$) $(\Delta\dot{\varepsilon}/\Delta\dot{\varepsilon})_{max}=1.376$ (run$_{B/N}$)	Transcutaneous extensometer with two pins	7 (M)	23–50[d]
Milgrom et al. (2000a)	Medial tibial mid-shaft cortex	Walk, run, stationary bicycling, leg press, stepping	$\varepsilon_{1min}=271$ (bicycle) $\varepsilon_{1max}=1378$ (run$_S$) $\varepsilon_{2min}=-291$ (bicycle) $\varepsilon_{2max}=-1675$ (run$_S$) $\gamma_{min}=628$ (bicycle) $\gamma_{max}=5027$ (run$_S$)	$\dot{\varepsilon}_{1min}=1258$ (leg press) $\dot{\varepsilon}_{1max}=8225$ (run$_S$) $\dot{\varepsilon}_{2min}=-1510$ (bicycle) $\dot{\varepsilon}_{2max}=-9766$ (run$_S$) $\dot{\gamma}_{min}=4480$ (bicycle) $\dot{\gamma}_{max}=38{,}164$ (run$_S$)	30° three rosette staple strain gages	6 (4M, 2F)	27–52[d]
Milgrom et al. (2000b)	Medial tibial mid-shaft cortex	Run, drop jump from 26, 39 and 52 cm heights	$\varepsilon_{1min}=896$ (jump$_{S26}$) $\varepsilon_{1max}=1415$ (run$_S$) $\varepsilon_{2min}=-1905$ (jump$_{S26}$) $\varepsilon_{2max}=-2104$ (run$_S$) $\gamma_{min}=5311$ (jump$_{S52}$) $\gamma_{max}=7370$ (Jump$_{S26}$)	$\dot{\varepsilon}_{1min}=4796$ (jump$_{S52}$) $\dot{\varepsilon}_{1max}=7780$ (run$_S$) $\dot{\varepsilon}_{2min}=-8663$ (jump$_{S52}$) $\dot{\varepsilon}_{2max}=-14{,}543$ (run$_S$) $\dot{\gamma}_{min}=28{,}493$ (jump$_{S52}$) $\dot{\gamma}_{max}=50{,}890$ (jump$_{S26}$)	30° three rosette staple strain gage	6 (4M, 2F)	27–52[d]
Milgrom et al. (2000c)	Medial tibial mid-shaft cortex	Run, walk, basketball rebound	$\varepsilon_{1min}=707$ (walk$_S$) $\varepsilon_{1max}=1592$ (rebound) $\varepsilon_{2min}=-561$ (walk$_S$) $\varepsilon_{2max}=-3163$ (rebound) $\gamma_{min}=1228$ (walk$_S$) $\gamma_{max}=9096$ (rebound)	$\dot{\varepsilon}_{1min}=3662$ $\dot{\varepsilon}_{1max}=8438$ (rebound) $\dot{\varepsilon}_{2min}=-4312$ (walk$_S$) $\dot{\varepsilon}_{2max}=-18{,}883$ (rebound) $\dot{\gamma}_{min}=12{,}578$ (walk$_S$) $\dot{\gamma}_{max}=57{,}876$ (rebound)	30° three rosette staple strain gages	3 (M)	37–52[d]
Milgrom et al. (2001a)	Medial tibial mid-shaft cortex	Walk, jog, vertical jump on two legs to 5 cm, vertical jump on one leg to 5 cm, stand broad jump to 20 cm, hop 50 cm on one leg, zig-zag hop on one leg	*At male subject* $\varepsilon_{1min}=600$ (jump$_{V2}$) $\varepsilon_{1max}=2180$ (jog$_S$) $\varepsilon_{2min}=-250$ (walk$_S$) $\varepsilon_{2max}=-490$ (jog$_S$) $\gamma_{min}=350$ (jump$_{V1}$) $\gamma_{max}=1490$ (hop$_{Z1}$) *At female subject* $\varepsilon_{1min}=500$ (jog$_S$) $\varepsilon_{1max}=1150$ (hop$_{Z1}$) $\varepsilon_{2min}=-550$ (walk$_S$) $\varepsilon_{2max}=-2240$ (hop$_{Z1}$) $\gamma_{min}=1250$ (walk$_S$) $\gamma_{max}=4240$ (hop$_{150}$)	*At male subject* $\dot{\varepsilon}_{1min}=2900$ (jump$_{V2}$) $\dot{\varepsilon}_{1max}=16{,}000$ (jog$_S$) $\dot{\varepsilon}_{2min}=-1900$ (walk$_S$) $\dot{\varepsilon}_{2max}=-6000$ (hop$_{Z1}$) $\dot{\gamma}_{min}=5000$ (walk$_S$) $\dot{\gamma}_{max}=15{,}600$ (hop$_{Z1}$) *At female subject* $\dot{\varepsilon}_{1min}=2450$ (jump$_{V2}$) $\dot{\varepsilon}_{1max}=4500$ (hop$_{Z1}$) $\dot{\varepsilon}_{2min}=-5000$ (walk$_S$) $\dot{\varepsilon}_{2max}=-8000$ (hop$_{150}$) $\dot{\gamma}_{min}=10{,}050$ (walk$_S$) $\dot{\gamma}_{max}=25{,}000$ (hop$_{150}$)	30° three rosette staple strain gages	2 (1M, 1F)	39, 33
Milgrom et al. (2001b)	Medial tibial mid-shaft cortex	Walk with shoes with different shoe soles	$\varepsilon_{1min}=464$ (walk$_{TS75}$) $\varepsilon_{1max}=721$ (walk$_{TS65A}$) $\varepsilon_{2min}=-700$ (walk$_{TS65A}$) $\varepsilon_{2max}=-1195$ (walk$_{TS75}$) $\gamma_{min}=1250$ (walk$_{TS65A}$) $\gamma_{max}=2628$ (walk$_{TSC}$)	$\dot{\varepsilon}_{1min}=2828$ (walk$_{TS75}$) $\dot{\varepsilon}_{1max}=3982$ (walk$_{TS65A}$) $\dot{\varepsilon}_{2min}=-6220$ (walk$_{TS75}$) $\dot{\varepsilon}_{2max}=-6507$ (walk$_{TS65A}$) $\dot{\gamma}_{min}=11{,}939$ (walk$_{TS65A}$) $\dot{\gamma}_{max}=16{,}121$ (walk$_{TSC}$)	30° three rosette staple strain gages	3 (M)	35–50[d]
Milgrom et al. (2002)[e]	Medial tibial mid-shaft cortex	Walk, jog, broad jump, vertical jump on one leg to 10 cm, vertical jump on two legs to 10 cm	*With shoes* $\varepsilon_{xmin}=185$ (walk$_{TS}$) $\varepsilon_{xmax}=1858$ (jump$_{V2}$) $\varepsilon_{ymin}=-359$ (jog$_{TS}$) $\varepsilon_{ymax}=-748$ (walk$_{TS}$) *Without shoes* $\varepsilon_{xmin}=160$ (walk$_{TB}$) $\varepsilon_{xmax}=1246$ (jog$_{TB}$) $\varepsilon_{ymin}=-361$ (walk$_{TB}$) $\varepsilon_{ymax}=-703$ (jog$_{TB}$)	*With shoes* $\dot{\varepsilon}_{xmin}=2943$ (walk$_{TS}$) $\dot{\varepsilon}_{xmax}=10{,}020$ (jog$_{TS}$) $\dot{\varepsilon}_{ymin}=-2028$ (jog$_{TS}$) $\dot{\varepsilon}_{ymax}=-3795$ (jog$_{TS}$) *Without shoes* $\dot{\varepsilon}_{xmin}=2102$ (walk$_{TB}$) $\dot{\varepsilon}_{xmax}=14{,}034$ (jog$_{TB}$) $\dot{\varepsilon}_{ymin}=-3504$ (walk$_{TB}$) $\dot{\varepsilon}_{ymax}=-5905$ (jog$_{TB}$)	90° two staple strain gages	2 (M)	40, 54

Table 1 (*continued*)

Study	Location of measurement	Exercise	Strain (μstrain)[b]	Strain rate (μstrain/s)[b]	Techniques	Sample size (gender)[c]	Age (years)
Ekenman et al. (2002)	Medial tibial mid and distal shaft cortex	Walk, run with sport and army shoes with different orthoses	$\Delta\varepsilon_{min} = 1005$ ($walk_{TBS}$) $\Delta\varepsilon_{max} = 2375$ (run_{TBSR})	$\dot{\varepsilon}_{xmin} = 4187$ ($walk_{TBS}$) $\dot{\varepsilon}_{xmax} = 15{,}668$ (run_{TBSR}) $\dot{\varepsilon}_{ymin} = -3115$ ($walk_{TSS}$) $\dot{\varepsilon}_{ymax} = -10{,}298$ (run_{TAB})	90° two staple strain gages	9	26–40[d]
Milgrom et al. (2003)	Medial tibial mid-shaft cortex	Ground and treadmill run	$\varepsilon_{xmin} = 648$ (run_{ST}) $\varepsilon_{xmax} = 1273$ (run_{SG}) $\varepsilon_{ymin} = -417$ (run_{ST}) $\varepsilon_{ymax} = -2456$ (run_{SG})	$\dot{\varepsilon}_{xmin} = 3175$ (run_{ST}) $\dot{\varepsilon}_{xmax} = 17{,}289$ (run_{SG}) $\dot{\varepsilon}_{ymin} = -2674$ (run_{ST}) $\dot{\varepsilon}_{ymax} = -14{,}880$ (run_{SG})	Single staple strain gage	3 (2M, 1F)	23–54[d]
Milgrom et al. (2007)	Medial tibial mid-shaft cortex	Walk, post fatiguing exercise protocol run, post fatiguing exercise protocol march	$\varepsilon_{xmin} = 394$ ($walk_{S}$) $\varepsilon_{xmax} = 558$ ($march_{SPF}$) $\varepsilon_{ymin} = -513$ ($march_{SPF}$) $\varepsilon_{ymax} = -672$ ($walk_{S}$)	$\dot{\varepsilon}_{xmin} = 4683$ ($walk_{S}$) $\dot{\varepsilon}_{xmax} = 5391$ (run_{SPF}) $\dot{\varepsilon}_{ymin} = -3820$ ($walk_{S}$) $\dot{\varepsilon}_{ymax} = -4615$ ($march_{SPF}$)	30° three rosette staple strain gages	4 (M)	27–52[d]
Arndt et al. (2003)	Dorsal surface of 2nd metatarsal shaft cortex	Walk with and without 20 kg load pre and post-fatigue protocol	*With 20 kg load* $\varepsilon_{xmin} = 142$ ($walk_{TBPO}$) $\varepsilon_{xmax} = 435$ ($walk_{TBPR}$) $\varepsilon_{ymin} = -2187$ ($walk_{TBPR}$) $\varepsilon_{ymax} = -2327$ ($walk_{TBPO}$) *Without 20 kg load* $\varepsilon_{xmin} = 174$ ($walk_{TBPO}$) $\varepsilon_{xmax} = 376$ ($walk_{TBPR}$) $\varepsilon_{ymin} = -1534$ ($walk_{TBPR}$) $\varepsilon_{ymax} = -2166$ ($walk_{TBPO}$)	*With 20 kg load* $\dot{\varepsilon}_{ymin} = -5030$ ($walk_{TBPO}$) $\dot{\varepsilon}_{ymax} = -5458$ ($walk_{TBPR}$) *Without 20 kg load* $\dot{\varepsilon}_{ymin} = -4165$ ($walk_{TBPR}$) $\dot{\varepsilon}_{ymax} = -4655$ ($walk_{TBPO}$)	90° two staple strain gages	8 (M)	45 ± 10[f]
Milgrom et al. (2002)[e]	Dorsal surface of 2nd metatarsal mid-shaft cortex	Walk, jog, broad jump, vertical jump on one leg to 10 cm, vertical jump on two legs to 10 cm	*With shoes* $\varepsilon_{xmin} = 416$ (jog_{TS}) $\varepsilon_{xmax} = 4551$ ($jump_{B}$) $\varepsilon_{ymin} = -934$ ($walk_{TS}$) $\varepsilon_{ymax} = -3734$ ($jump_{B}$) *Without shoes* $\varepsilon_{xmin} = 234$ ($walk_{TB}$) $\varepsilon_{xmax} = 1109$ (jog_{TB}) $\varepsilon_{ymin} = -2685$ ($walk_{TB}$) $\varepsilon_{ymax} = -5315$ (jog_{TB})	*With shoes* $\dot{\varepsilon}_{xmin} = 2647$ (jog_{S}) $\dot{\varepsilon}_{xmax} = 7608$ ($walk_{TS}$) $\dot{\varepsilon}_{ymin} = -5742$ ($walk_{TS}$) $\dot{\varepsilon}_{ymax} = -17290$ (jog_{TS}) *Without shoes* $\dot{\varepsilon}_{xmin} = 3372$ ($walk_{TB}$) $\dot{\varepsilon}_{xmax} = 12{,}062$ (jog_{TB}) $\dot{\varepsilon}_{ymin} = -9752$ ($walk_{TB}$) $\dot{\varepsilon}_{ymax} = -46{,}150$ (jog_{TB})	90° two staple strain gages	2 (M)	40, 54
Arndt et al. (2003)	Dorsal surface of 2nd metatarsal proximal shaft cortex	Pre- fatiguing protocol walk, post fatiguing protocol walk	$\varepsilon_{xmin} = 200$ ($walk_{TLPR90}$) $\varepsilon_{xmax} = 706$ (wal_{TLPO59}) $\varepsilon_{ymin} = -1050$ ($walk_{TLPR59}$) $\varepsilon_{ymax} = -2370$ ($walk_{TLPR59}$)	$\dot{\varepsilon}_{ymin} = -2400$ ($walk_{TLPR59}$) $\dot{\varepsilon}_{ymax} = -5900$ ($walk_{TLPO59}$)	90° two staple strain gages	6	45 ± 12[f]
Perusek (2004)	Calcaneous cortex	Walk	$\varepsilon_{1max} = 5500$ ($walk_{TB}$) $\varepsilon_{2max} = -6000$ ($walk_{TB}$)	–	Transcutaneous delta extensometer	1 (M)	–
Aamodt et al. (1997)	Proximal lateral aspect of the femoral cortex	Walk, one and two legged stance, stair climb	*At subject one 49 years* $\varepsilon_{xmin} = 121$ ($stance_{2}$) $\varepsilon_{xmax} = 1441$ ($stance_{1}$) $\varepsilon_{1min} = 304$ ($stance_{2}$) $\varepsilon_{1max} = 1463$ ($stance_{1}$)	–	120° three rosette surface strain gages	2 (F)	24, 49

			$\varepsilon_{2min} = -347$ (stance$_2$) $\varepsilon_{2max} = -948$ (stair climb) *At subject two 24 years* $\varepsilon_{xmin} = 378$ (stance$_2$) $\varepsilon_{xmax} = 1196$ (stance$_1$) $\varepsilon_{1min} = 494$ (stance$_2$) $\varepsilon_{1max} = 1225$ (stance$_1$) $\varepsilon_{2min} = -60$ (stance$_1$) $\varepsilon_{2max} = -194$ (stair climb)				
Földhazy et al. (2005)	Dorsal surface of distal radius metaphysic cortex	Arm (biceps) curl with 7 kg weight, chin-up hanging on an iron bar (hands in supination), fall forward from standing and landing on extended hands, fall forward from kneeling and landing on extended hands, push up on knees, stir a pot of dough with a wooden ladle, type writing, vacuum a carpet, wrist curl in extension with 2 kg weight, wrist curl in flexion with 2 kg weight	$\varepsilon_{xmin} = 500$ (type writing) $\varepsilon_{xmax} = 1420$ (chin$-$up) $\varepsilon_{ymin} = -300$ (type writing) $\varepsilon_{ymax} = -6000$ (fall$_{FSH}$)	$\dot{\varepsilon}_{ymin} = -1000$ (wrist curl$_{E2}$) $\dot{\varepsilon}_{ymax} = -85{,}500$ (fall$_{FSH}$)	90° two staple strain gages	10 (F)	47 ± 13[f]
Szivek et al. (2005)	Lamina of the thoracic T9, T10, and T11 vertebrae cortex	Bend, twist, sit down, stand up, lie down from sitting, climb off table, walk, stair climb, back pack lift	*At T9* $\varepsilon_{xmin} = 40$ (lie down) $\varepsilon_{xmax} = 1350$ (stair cimb) *At T10* $\varepsilon_{xmin} = 145$ (lie down) $\varepsilon_{xmax} = 1795$ (stair climb) $\varepsilon_{ymin} = -300$ (back pack$_L$) $\varepsilon_{ymax} = -900$ (stand up) *At T11* $\varepsilon_{xmin} = 115$ (lie down) $\varepsilon_{xmax} = 1595$ (stair climb) $\varepsilon_{ymin} = -225$ (climb off$_T$) $\varepsilon_{ymax} = -1450$ (twist$_{CW}$)	–	Calcium phosphate ceramic coated single surface strain gage	1 (F)	17
Asundi and Kishen (2000)	Dental alveolar cortex and tooth root surface	Bite force 50 N	*At cervical region of alveolar* $\varepsilon_{xmin} = 135$ $\varepsilon_{xmax} = 352$ $\varepsilon_{ymin} = -42$ $\varepsilon_{ymax} = -100$ $\gamma_{xymin} = 5$ $\gamma_{xymax} = -55$		45° three rosette surface strain gage	2 (M)	–

Table 1 (*continued*)

Study	Location of measurement	Exercise	Strain (μstrain)[b]	Strain rate (μstrain/s)[b]	Techniques	Sample size (gender)[c]	Age (years)
			At middle region of alveolar				
			$\varepsilon_{xmin}=35$				
			$\varepsilon_{xmax}=210$				
			$\varepsilon_{ymin}=-10$				
			$\varepsilon_{ymax}=-18$				
			$\gamma_{xymin}=5$				
			$\gamma_{xymax}=-47$				
			At apical region of alveolar				
			$\varepsilon_{xmin},\varepsilon_{xmax},\varepsilon_{ymin},\varepsilon_{xmax},\gamma_{xymin},\gamma_{xymax}=0$				
			At cervical region of tooth root				
			$\varepsilon_{xmax}=90$				
			$\varepsilon_{ymax}=125$				
			$\gamma_{xymax}=-290$				
			At middle region of tooth root				
			$\varepsilon_{xmax}=40$				
			$\varepsilon_{ymax}=-25$				
			$\gamma_{xymax}=-100$				
			At apical region of tooth root				
			$\varepsilon_{xmax},\varepsilon_{ymax},\gamma_{xymax}=0$				

ε_{xmin}: minimum normal tensile strain, ε_{xmax}: maximum normal tensile strain, ε_{ymin}: minimum normal compression strain, ε_{ymax}: maximum normal compression strain, γ_{xymin}: minimum normal shear strain, γ_{xymax}: maximum normal shear strain, ε_{1min}: minimum principal tensile strain, ε_{1max}: maximum principal tensile strain, ε_{2min}: minimum principal compression strain, ε_{2max}: maximum principal compression strain, γ_{min}: minimum principal shear strain, γ_{max}: maximum principal shear strain, $\Delta\varepsilon_{min}$: minimum peak to peak strain, $\Delta\varepsilon_{max}$: maximum peak to peak strain, $\Delta\varepsilon_{ave}$: average peak to peak strain, $(\Delta\varepsilon/\Delta\varepsilon)_{min}$: minimum percentage of peak to peak strain, $(\Delta\varepsilon/\Delta\varepsilon)_{max}$: maximum percentage of peak to peak strain.

$\dot{\varepsilon}_{xmin}$: minimum normal tensile strain rate, $\dot{\varepsilon}_{xmax}$: maximum normal tensile strain rate, $\dot{\varepsilon}_{ymin}$: minimum normal compression strain rate, $\dot{\varepsilon}_{ymax}$: maximum normal compression strain rate, $\dot{\varepsilon}_{imin}$: minimum principal tensile strain rate, $\dot{\varepsilon}_{1max}$: maximum principal tensile strain rate, $\dot{\varepsilon}_{2min}$: minimum principal compression strain rate, $\dot{\varepsilon}_{2max}$: maximum principal compression strain rate, $\dot{\gamma}_{min}$: minimum principal shear strain rate, $\dot{\gamma}_{max}$: maximum principal shear strain rate, $\dot{\varepsilon}_{yave}$: average of maximum normal compression strain rate, $(\Delta\dot{\varepsilon}/\Delta\dot{\varepsilon})_{min}$: minimum percentage of peak to peak strain rate, $(\Delta\dot{\varepsilon}/\Delta\dot{\varepsilon})_{max}$: maximum percentage of peak to peak strain rate.

Lower subscripts are sorted out alphabetically and they are as follows:

B: broad, B/N: infantry boot to Nike Air shoe, CW: clock-wise, F2: in flexion with 2 kg weight, FSH: fall forward from standing and landing on extended hands, L: lifting, LB: light infantry boot, RS: running shoes, S17: with shoes and load of 17 kg, S26: with shoes from 26 cm, S52: with shoes from 52 cm, S: with shoes, SCC: with shoes and cane contralaterally, SCI: with shoes and cane ipsilaterally, SD: with shoes downhill, SG: with shoes on ground, SL27: with shoes and load of 27 kg, SPF: with shoes and post-fatigue, SUZ: with shoes uphill zigzag, Srep: with shoes repetitive, Ssin: with shoes single, T: table, TAB: treadmill with army boot, TB: treadmill barefoot, TB/N: treadmill with infantry boot to Nike Air shoe, TBPO: treadmill barefoot post fatigue exercise, TBPR: treadmill barefoot pre-fatigue exercise, TBS: treadmill with boot+soft orthoses, TBSR: treadmill with boot+semi-rigid orthoses, TLPO59: treadmill with load post-fatigue exercise with army boot M59, TLPR59: treadmill with load pre-fatigue exercise with army boot M59, TLPR90: treadmill with load pre-fatigue exercise with army boot M90, TRWS: treadmill with Rockport walking shoes, TRS: treadmill with running shoes, TS: treadmill with shoes, TSC: treadmill with shoes with composite layers of shores, TSS: treadmill with shoes+semi rigid, TS65A: treadmill with shoes with 65 shore+air cell, TS75: treadmill with shoes with 75 shore, TTB: treadmill with two layer infantry boot, TZB: treadmill with Zohar boot, TZ/B: treadmill with Zohar boot to infantry boot, V1: vertical on one leg, V2: vertical on two legs, Z1: zigzag on one leg, ZB: Zohar boot, Z/B: Zohar boot to infantry boot, Z/N: Zohar boot to Nike Air shoe 1 on one leg, 2 on two legs, 150 on one leg at 50 cm.

[a] The reported strain results are relevant only to the small area of the bone surface under investigation and may not reflect other anatomical sites on the same bone which might experience minimum or maximum strain.

[b] Unless specified the maximum and minimum strain and strain rates were reported from each study.

[c] M denotes male and F denotes female.

[d] Range of age.

[e] The study of Milgrom et al. (2000a,b,c) investigated simultaneously the tbial and 2nd metatarsal strains.

[f] Mean age.

pathological overload zone and therefore increases the risk of stress fracture. Moreover, it is not clear whether running maintains or increases bone strength. This is due to the fact that among the studies, which measured tibial strains during running, five studies (Lanyon et al., 1975; Burr et al., 1996; Milgrom et al., 1996, 2002; Ekenman et al., 1998) reported strain magnitudes between 277 and 1583 $\mu\varepsilon$ all of which fall in the physiological loading zone. Playing basketball decreased tibial stress fracture risk in infantry recruits who played basketball regularly for at least 2 years before basic training (Milgrom et al., 2000c). To understand the reason, Milgrom et al. (2000c) measured in vivo strains and strain rates that occur during basketball rebounding and compared them to walking and running. They found that tibial strains and strain rates produced during basketball rebounding were significantly higher than those produced during running and walking. Ekenman et al. (1998) studied the tibial strains during different exercises at two different prevalent sites for stress fracture in athletes and soldiers: antero-medial aspect of the tibial cortex mid-shaft and postero-medial aspect of the distal tibial cortex shaft. Their study reported different tibial strains at these two sites during different exercises with a significant increase of compressive principal strains at the postero-medial aspect of the distal tibial cortex shaft. The maximum and minimum values of strains and strain rates reported from in vivo tibial strain measurement studies with their corresponding activities are shown in Figs. 3 and 4, respectively.

The effect of muscle fatigue following strenuous exercise on the tibial strains was investigated in the studies of Milgrom et al. (2007) and Fyhrie et al. (1998). These studies reported a

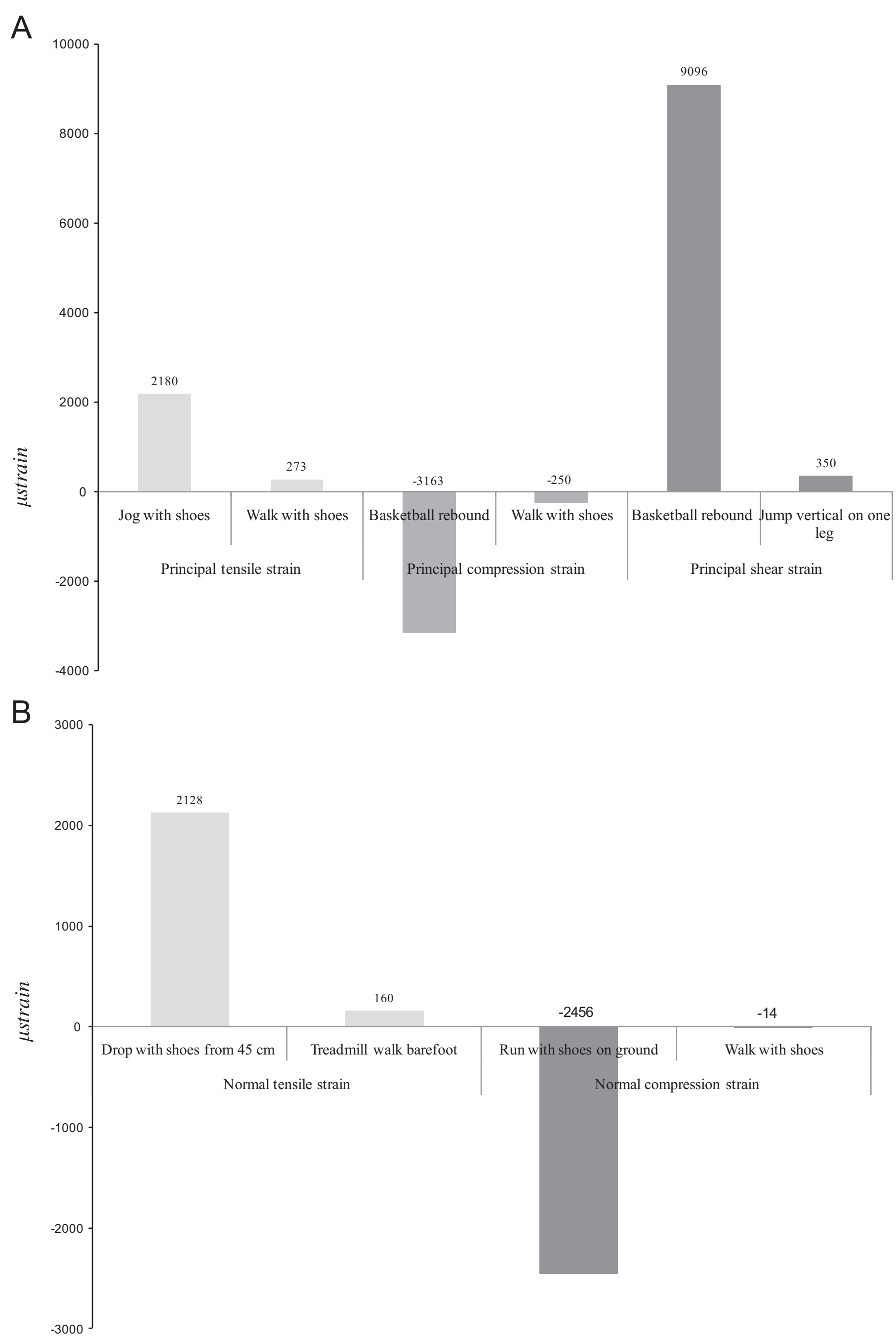

Fig. 3. Maximum and minimum values of tibial strains with their corresponding activities reported by in vivo strain measurement studies: (A) principal strains and (B) normal axial strains.

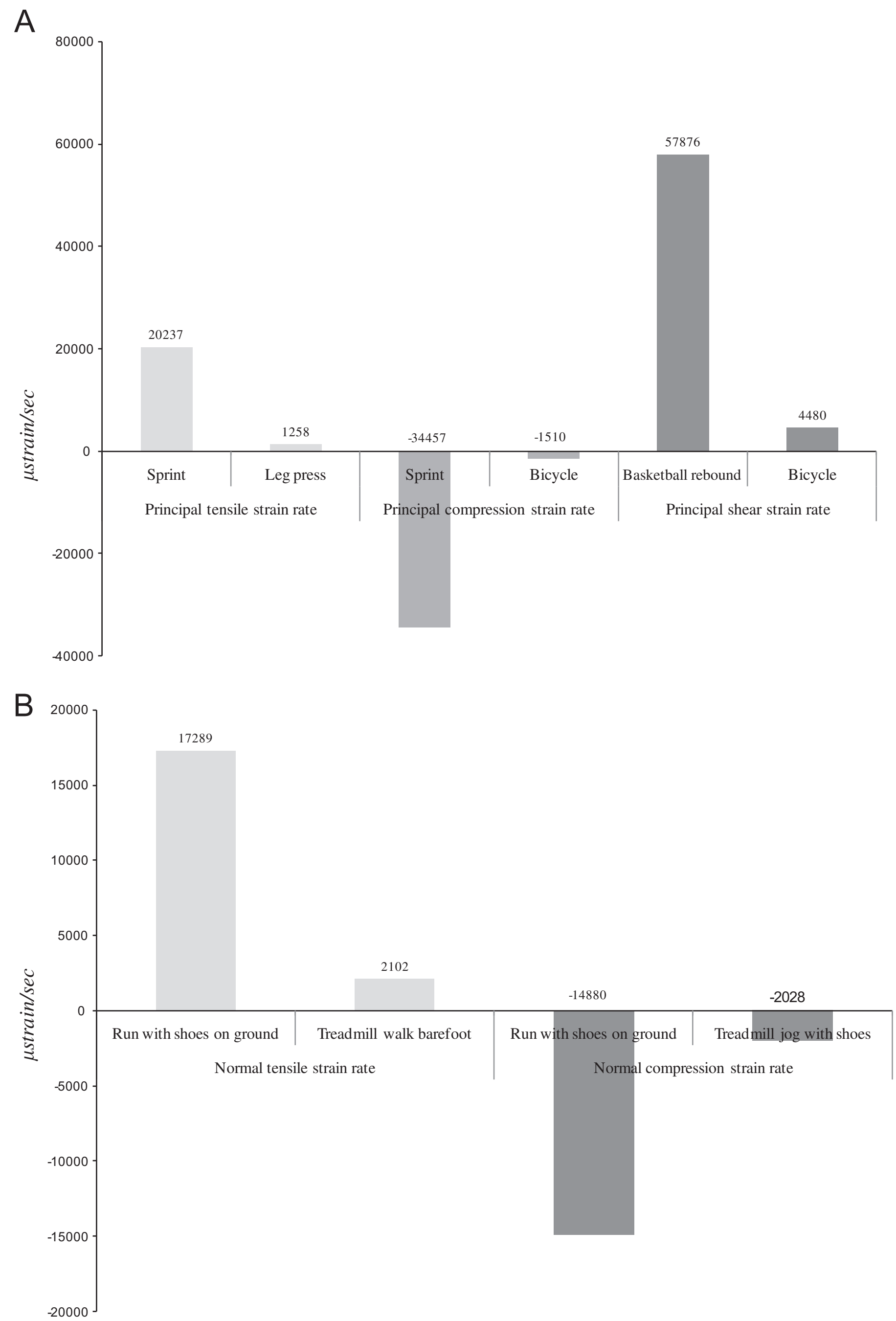

Fig. 4. Maximum and minimum values of tibial strain rates with their corresponding activities reported by in vivo strain measurement studies: (A) principal strain rates and (B) normal axial strain rates.

significant change in strain rate and a non significant change in strain magnitude due to muscle fatigue. Milgrom et al. (2007) showed an increase in axial strain rates and axial tensile strains and decrease in compression strains after muscle fatigue. Fyhrie et al. (1998) found that the bone strain rate increase in younger people is greater compared to older people following fatiguing protocol. However, due to the limited sample in the study of Fyhrie et al. (1998) we might not agree to that the change of strains and strain rates after muscle fatigue is age dependent.

Preventing tibial stress fractures requires knowledge of the risk factors that predispose to this injury. Therefore, a number of tibial strain measurement in vivo studies were conducted in an attempt to evaluate the role of shoes, type of surface and use of cane in lowering strains and strain rate and thus reduce the risk of tibial stress fracture. Ekenman et al. (2002) and Milgrom et al. (1996) found that different types of shoes produced different values of tibial strains and strain rates during walking and running. Milgrom et al. (2003) reported higher tibial strain and strain rates in running over ground than running on treadmill. Using a cane either ipsilaterally or contralaterally during walking was shown to significantly lower strain rates during walking compared to walking without it (Mendelson et al., 1998).

4.1.2. Second metatarsal

Metatarsal fractures are the most common bone related foot injuries (Burr and Milgrom, 2001). These fractures are common in athletes and infantry recruits and are commonly known as “march fractures” (Milgrom et al., 2002). In particular, the second metatarsal is most commonly affected with the stress fracture caused by overuse (Burr and Milgrom, 2001). To better understand metatarsal stress fracture etiology, in vivo strain measurements were conducted at the dorsal surface of the second metatarsal diaphysis. Milgrom et al. (2002) investigated strains and strain rates at medial tibia and second metatarsal simultaneously during different activities. They found that second metatarsal experienced higher strain and strain rates than medial tibia particularly in the compression direction. This study supported the observation of the development of earlier fracture of second metatarsal in infantry recruits compared to tibial fracture, which take longer time to develop. Arndt and colleagues performed two direct in vivo experiments to measure strain on second metatarsal. In their first study (Arndt et al., 2002) they investigated the effect of muscle fatigue and load carrying on second metatarsal strains during walking barefoot. They found that normal compression strain increased significantly in the fatigue state during walking with and without load compared to non-fatigue state, while on the other hand normal tensile strain decreased in the fatigue state. In a follow up study (Arndt et al., 2003), they investigated the effect of two types of military footwear on second metatarsal strains during fatiguing protocol to determine the optimal one for reducing the risk of stress fractures of the second metatarsal. None of the in vivo studies conducted at second metatarsal used three strain gages, and therefore, they were unable to provide principal strains and their directions. The normal tensile strains reported in the in vivo strain measurement studies at second metatarsal (142–1109 $\mu\varepsilon$) were within the physiological loading zone defined by the mechanostat theory except for normal tensile strains during jumping (Milgrom et al., 2002), which were within the overload zone. The compression axial strains were generally within the overload zone.

4.1.3. Calcaneus

Perusek (2004) proposed a new design of extensometer consisting of three pins as a potentially valuable research tool for measuring bone strains in vivo. The main advantage of his new design over other extensometers is its capability of obtaining principal strains. He applied his new extensometer design to measure calcaneus strains in vivo during treadmill barefoot walking. The maximum principal strains reported in his study (5500–6000 $\mu\varepsilon$) fall within the pathological overload zone defined by the mechanostat theory, which might explain the common stress fractures in this site (Burr and Milgrom, 2001) when walking barefoot.

4.1.4. Lateral proximal femur

Aamodt et al. (1997) measured in vivo strains at the right proximal lateral aspect of the femoral cortex in two female patients undergoing surgery for snapping hip syndrome. For that, they glued rosette surface strain gages to every patient femur about 43 and 39 mm distal to the greater trochanter with corresponding neck–shaft angles of 124° and 135°, respectively. The study was performed to determine whether the lateral aspect of femoral cortex is under tension or compression during normal activity. The study revealed that tensile strains were consistently recorded on the proximal lateral femur during several loading situations of the lower extremity. The highest recorded strains were during one legged stance while two legged stance produced the lowest strains. The reported strains in this study during all performed activities (121–1463 $\mu\varepsilon$) were within the physiological loading zone defined by the mechanostat theory.

4.1.5. Distal radius

Distal radius fracture is the most common bone fracture of the radius in the forearm due to osteoporosis (Földhazy et al., 2005). To characterize the ability of various forms of exercise regimes to bone strengthening process, in vivo distal radius strain measurements were performed by Földhazy et al. (2005) on ten female subjects. They found that performing push up and falling forward on extended hands generated significant increase in compression strain while falling forward on extended hands generated significant increase in compression strain rate compared to other exercises. Földhazy et al. (2005) used two strain gages, and therefore, principal strains were not reported. All strains produced by the investigated exercises in this study except for the compression strains produced by falling forward on extended hands and push up were between 300 and 1750 $\mu\varepsilon$, which are within the physiological loading zone defined by the mechanostat theory. Falling forward on extended hands and push up generated strains between 5000 and 6000 $\mu\varepsilon$, which fall in the pathological overload zone, and therefore, these exercises are at higher risk of developing distal radius stress fractures.

4.1.6. Lamina of vertebra

Szivek et al. (2005) evaluated the lamina strains in vivo in a female patient who underwent surgery to facilitate spine fusion during standard daily activities to determine potential risk associated with each activity in the postoperative period. They used an implantable monitoring system consisting of strain gages bonded to lamina and a radio telemetry unit. Prior to applying this implantable system in vivo, they tested it on cadaver spines in vitro (Szivek et al., 2002). Lamina strains were monitored during daily activities for seven months after the surgery while fusion was occurring. Calcium phosphate ceramic (CPC) coated strain gages were developed to allow long-term in vivo strain measurements. A single strain gage was used at each of the three vertebrae investigated, and therefore, the study was limited to report axial strains. The highest lamina strains were recorded during stair climbing while the lowest strains were during lying down from sitting. Based on the mechanostat theory, the reported lamina strains during standard daily activities (40–1795 $\mu\varepsilon$) were within the physiological loading zone.

4.1.7. Alveolar and tooth root

The development of dental implants is a challenging biomedical engineering task that depends on several factors including implant design, synthetic materials, geometry, fixation methods and osseointegration (Carvalho et al., 2004). An insight into the stress and strain distribution on alveolar and tooth root surface can provide a better understanding of the tooth function under physiological loading and thus assist in the clinical success of dental implant design. For this reason, Asundi and Kishen (2000) have performed a direct measurement of strains in the alveolar bone region and tooth root surface in two patients who underwent dental surgery using surface mounted strain gage to evaluate the strains under bite force. They found that the alveolar bone was subjected to significantly higher axial tensile strains compared to those of tooth root surface, while tooth root surface was subjected to significantly higher compression axial strains compared to those of the alveolar bone. The highest recorded strains were at the cervical region of the alveolar bone and tooth root surface (352 $\mu\varepsilon$) and were within the physiological loading zone defined by the mechanostat theory.

4.2. In vivo strains in different bones during walking

A comparison between in vivo strain values in different bones during similar exercise might be interesting regardless of anthropometric variables and experimental techniques variety involved in the in vivo strain measurement studies. We found that barefoot

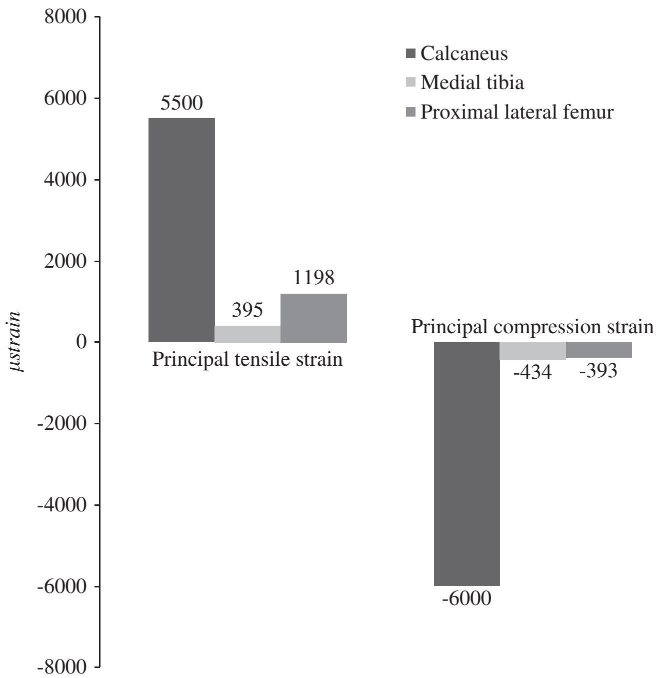

Fig. 5. Principal tensile and compression strains at the calcaneus, medial tibia and proximal lateral femur during barefoot walking.

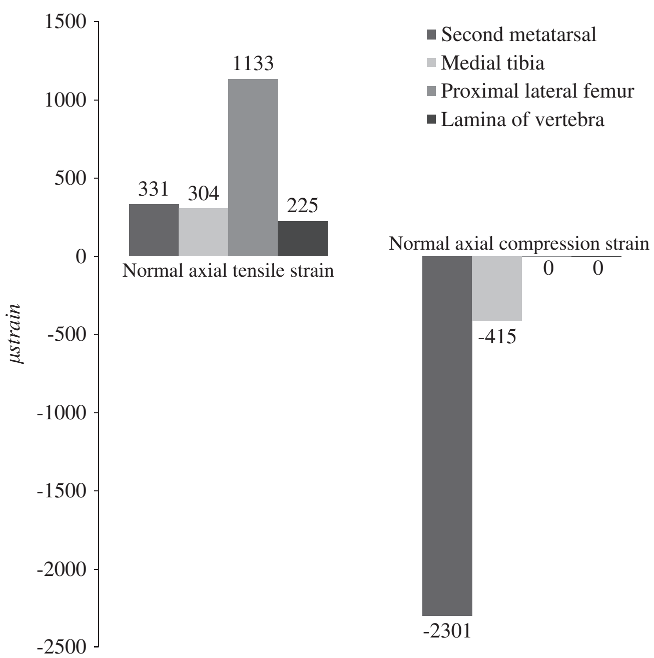

Fig. 6. Normal axial tensile and compression strains at the second metatarsal, medial tibia, proximal lateral femur and lamina of vertebra during barefoot walking.

walking on a level was the most common exercise investigated by the in vivo strain measurement studies. Fig. 5 shows principal tensile and compression strains measured in vivo at medial tibia (Lanyon et al., 1975), proximal lateral femur (Aamodt et al., 1997) and calcaneus (Perusek, 2004) during barefoot walking. Fig. 6 shows normal axial tensile and compression strains measured in vivo at medial tibia (Milgrom et al., 2002), second metatarsal (Arndt et al., 2002; Milgrom et al., 2002), proximal lateral femur (Aamodt et al., 1997) and lamina of vertebra (Szivek et al., 2005) during barefoot walking.

It can be depicted from Fig. 5 that the calcaneus was exposed to significantly higher principal strains during barefoot walking compared with their correspondences at medial tibia and proximal lateral femur. According to the mechanostat theory, barefoot walking will expose the calcaneus to higher risk of stress fracture. Therefore wearing shoes might reduce the strains and thus reduce the risk of stress fracture. Yet, barefoot walking generated strains at medial tibia and proximal lateral femur within the physiological loading zone in which the bone strength is maintained. Fig. 6 shows that proximal lateral femur was subjected to the highest tensile normal axial strains while second metatarsal was subjected to the highest compression normal axial strain during barefoot walking. Based on the mechanostat theory, strains generated during barefoot walking were within the physiological loading zone except for the normal compression strain at second metatarsal, which exceeded to overload zone.

4.3. *Bone adaptation*

Mechanical loading is one of the key factors that stimulates bone adaptation. The bone's functional adaptation to mechanical loading environment stimuli depends primarily on several factors including strain magnitude, strain rate, strain distribution, strain cycle and loading frequency (Cullen et al., 2001). The bone adaptation is influenced by the interaction of these factors (Cullen et al., 2001). Understanding how these factors interact with each other to influence bone adaptation may clarify how bone functional adaptation can be optimized and may help to develop effective exercise regimes to improve skeletal rigidity (Zernicke et al., 2006). The measurements of in vivo bone strain may be the first major step to reveal the mechanical strain conditions in vivo and help us understanding how these factors interact with each other to benefit skeletal adaptation.

4.3.1. *Strain magnitude and strain rate*

Strain magnitude is the amount of relative bone deformation due to mechanical loading while strain rate is the change of strain magnitude per second. It has been shown that dynamic strains rather than static strains are the primary stimulus of the functional adaptation of a bone (Turner, 1998). High strain magnitudes together with high strain rates are major determinates for a positive adaptive bone response (Martin and Burr, 1989). Evidence from animal studies have shown that in order to get a positive bone adaptive response, high strain rate and magnitude are essential (Umemura et al., 1995; Turner et al., 1995). In vivo strain measurement studies conducted at human tibia and distal radius showed that vigorous activities, which elicit high forces, such as running, jumping, basketball rebounding and push up generated higher strain magnitudes and rates compared to other light activities. Therefore, on the basis of higher strain magnitudes and rates, these vigorous activities might have higher potential to influence adaptive remodeling to strengthen the bone. However, based on the mechanostat theory, high strain magnitudes greater than 4000 $\mu\varepsilon$ might result in a negative adaptive bone response in which bone suffers microdamage and unorganized bone is added as a part of the repair process. A limitation of the mechanostat theory is that it is based on strain magnitudes and neglects the other adaptation factors. Further in vivo bone strain measurement studies are required to determine the specific dose of strain magnitude and rate together in relation with adaptive bone response.

4.3.2. *Strain distribution*

Bone strain distribution denotes the way strain is distributed across a section of bone. The more unusual the strain distribution, the more adaptive response of growing bone to dynamic loading (Lanyon, 1996). Measuring the strain distribution requires measuring the strain at different sites across the bone section, which is highly challenging to be done in vivo using the current strain measurements techniques due to their invasiveness. Using three strain gages rosette will allow the measurement of the strain direction at a single point that is the angle between the principal axis and the axis of measurement. Some of the in vivo strain measurement studies conducted on medial tibia (Milgrom et al., 2000a, 2001a) measured strain direction to figure out the strain distribution across the medial tibial section. They assumed that the strain distribution has unusual pattern if there is a significant variation of the strain direction during exercise (Milgrom et al., 2000a; Milgrom et al., 2001b). To our knowledge, their assumption has not been verified yet, and it is limited since the measurement of the strain direction is only relevant to one site and might not be valid to other sites across the bone section.

High strain magnitudes and rates that occur during basketball rebounding is not the only reason that makes this exercise elicit maximal bone adaptation compared to running and walking (Milgrom et al., 2000c). Varying unusual strain distribution produced during basketball rebounding is an additional reason. On the basis of strain distribution, zigzag hopping (Milgrom et al., 2001a), zigzag running (Burr et al., 1996) and basketball rebounding (Milgrom et al., 2000c) were the only multidirectional exercises investigated by in vivo strain measurement studies that have potential for positive adaptive bone response.

4.3.3. Strain cycle and loading frequency

Strain cycles refer to the number of loading cycles required for bone to change its formation at a given magnitude, whereas loading frequency denotes the number of strain cycles per second. Based on the in vivo strain measurement in human bone, the bone is unlikely to fail due to fatigue during physical activities. In vitro mechanical testing has shown that cortical bone will fail in tension by fatigue within 10^3–10^6 loading cycles at strain range of 5000–10,000 $\mu\varepsilon$ or within 10^6 loading cycles at 3000 $\mu\varepsilon$ (Carter et al., 1981). A number of animal studies (Rubin and Lanyon, 1984; Umemura et al., 1997) have provided evidence that there is a threshold number of cycles above which additional loading cycles produce no additional bone adaptation. Qin et al. (1998) showed that at a high loading frequency as applied load or strain magnitude decreased, the number of strain cycles required for activation of formation increased. They showed that the strain threshold magnitude required to activate bone formation decreased to as low as 70 $\mu\varepsilon$ with 108,000 applied loading cycles at a loading frequency of 30 Hz. On the other hand, Cullen et al. (2001) studied the dose-response relationship between strain cycles and strain magnitude at a low loading frequency of 2 Hz. They showed that as applied load or strain magnitude increases, the number of strain cycles required to initiate bone formation decreases. Another interesting issue is the number of cycles of different exercises required to stimulate similar bone adaptation. For example, how many cycles of jumping is required to produce equivalent bone adaptation produced during running a certain distance? Unfortunately, no information is available from in vivo strain measurement studies in human bone about the threshold number of cycles as well as the equivalent number of cycles of different exercises required to stimulate similar bone adaptation.

In the study conducted by Qin et al. (1998), they showed that the strain threshold magnitude required to activate bone formation decreased as loading frequency increased. The dose-response relationship between loading frequency and the bone formation response was addressed in some animal studies (Turner et al., 1994, 1995) in which it was shown that bone formation rate increased with the increasing loading frequency.

5. Conclusion

The majority of in vivo human bone strain measurement studies have been performed on the tibia due to its accessible location and its relevance as a common site for stress fracture in athletes and soldiers. Generally most of the strains measured in vivo in different bones were within the physiological loading zone defined by the mechanostat theory, which implies stimulation of remodeling process to maintain bone strength. Based on the tibial strain measurements during running, the evidence is not adequate to conclude that running stimulates bone modeling as defined by the mechanostat theory. The calcaneus was exposed to the highest strains during barefoot walking when compared with those of the medial tibia, lateral proximal femur, lamina of vertebra and second metatarsal. Dynamic impulsive exercises, such as sprinting, basketball rebounding and jumping produced the highest tibial strains and strain rates. A combined experimental in vivo strain measurement and computational approach is required to address some of the remaining research questions related to bone adaptation process. First, characterizing the relationship between the adaptive bone response and the dosages of strain magnitude and strain rate together. Second, defining the threshold number of cycles for a couple of daily exercises, such as running and walking. Third, determining the equivalent number of cycles of different exercises required to stimulate similar bone adaptation. Finally, designing exercise protocols to improve bone strength.

Conflict of interest statement

There is no potential conflict of interest. None of the authors received or will receive direct or indirect benefits from third parties for the performance of this study.

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Appendix A. Supplementary information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jbiomech.2011.08.004.

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